RING-EXPANSION CARBONYLATION OF EPOXIDES: DEVELOPMENT OF NEW CATALYSTS FOR IMPROVED REGIO- AND STEREOCONTROL

A Dissertation

Presented to the Faculty of the Graduate School

of Cornell University

In Partial Fulfillment of the Requirements for the Degree of

Doctor of Philosophy

by

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August 2013

RING-EXPANSION CARBONYLATION OF EPOXIDES: DEVELOPMENT OF NEW CATALYSTS FOR IMPROVED REGIO- AND STEREOCONTROL

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Cornell University 2013

Carbon monoxide is arguably one of the most important feedstocks in organic synthesis because it enables the introduction of valuable functional groups in often a mild, efficient, and economical manner. Utilization of this building block in hydroformylation reactions or ring-expansion carbonylation reactions of heterocycles gives rise to value added-products. One transformation of particular importance is the carbonylation of epoxides to β-lactones. β-Lactones are a highly versatile set of compounds that can undergo numerous reactions in often a benign and economical fashion, thus giving rise to small molecules such as aldol-type compounds, and polymers such as polyesters. The use of catalysts of the form [Lewis acid]$^+$[Co(CO)$_4$]$^-$ have streamlined the synthesis of β-lactones to a point where implementation on an industrial scale seems feasible. Nonetheless, challenges remain in the conversion of epoxides to β-lactones using these catalysts. Regioselectivity in the carbonylation of *cis*- or *trans*-disubstituted epoxides, and enantioselectivity in general are two largely unsolved synthetic hurdles in this regard and await further exploration.

The work presented herein introduces new catalyst design strategies, and implements them in an effort to address these remaining challenges. The result are four new carbonylation catalysts that enable the highly regioselective synthesis of β-

lactones starting from *cis*- or *trans*-disubstituted epoxides. The value of the resulting products, and the fact that regioselective ring-opening reactions of disubstituted epoxides have been a long-standing challenge in the field of organic synthesis make this study relevant on both a practical as well as an academic level.

In addition to the four catalysts introduced for improved regioselectivity, two more catalysts were synthesized and found to be competent for the formation of highly enantioenriched β-lactones starting from *meso* or *racemic* epoxides. Given the scarcity of catalysts that can affect similar transformations with equally high selectivities, this represents another important step forward in the field of ring-expansion carbonylation reactions.

Lastly, the use of carbon monoxide in a more streamlined synthesis of a pharmaceutically relevant class of compounds called ampakines is explored. This new methodology underlines once more the synthetic potential that rests in this building block.

BIOGRAPHICAL SKETCH

Michael F. Mulzer was born in 1983 in Rosenheim, Germany. He received a Diplom-degree in chemistry from the Humboldt University of Berlin in 2008, and subsequently enrolled for graduate studies at Cornell University, where he joined the research group of Geoffrey W. Coates. Upon graduation, he will return to Germany for a postdoctoral position at CaRLa.

ACKNOWLEDGMENTS

I would like to thank my advisor Prof. Geoffrey Coates for having been my guide on this incredible and fun journey that was graduate school. I learnt a lot during those five years under Geoff's guidance, and matured both as a person and a scientist. Geoff was always available and supported me in countless ways in and outside lab. I would not be where I am now without him.

Furthermore, I would like to thank all members of my committee, Prof. Bruce Ganem, Prof. Chad Lewis, and Prof. Paul Chirik, for all of their help, advice, and insight. Their doors were always open when I needed their support or sought scientific counsel, and I really appreciated the discussions that I had with each of you.

Kelly Case was an indispensable help in so many ways, and a lot of things would never have realized without her. Thanks Kelly!

None of my work would have been possible without the never-ending help and insight from Anne LaPointe, Ivan Keresztes, Anthony Condo, Emil Lobkovsky, and Prof. William Dichtel.

Working (and living) in the Coates group was an incredible experience. I appreciate all the help and guidance that I was lucky to receive from all my coworkers over the years, and none of this work would have been possible without them. Thank you! I also wish to thank all of my friends, past and present, new and old, for always being there for me, lending an ear, and helping me wherever and whenever possible.

Lastly, I want to thank Cathy DeBlase, and my family.

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CHAPTER ONE

Overview of Properties and Reactions of β-Lactones, and Current Challenges Associated with Their Synthesis

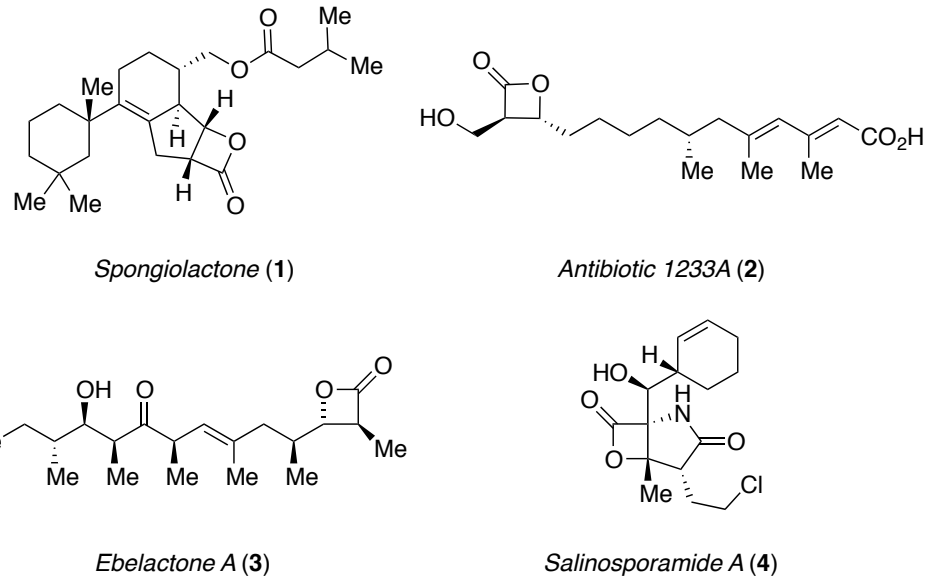
1.1 Introduction and General Properties of β-Lactones

β-Lactones, also known as 2-oxetanones, have been known to the chemical community since the late 1880's,[1,2] and have been valued as a versatile class of compounds ever since. Despite their inherent chemical reactivity, they are readily isolated and characterized. As one may expect, β-lactones are composed of a planar four-membered ring that displays IR absorptions around 1810-1840 cm^{-1}, which are characteristic of the carbonyl-functionality.[3] The planar structure is supported further by the ^{1}H NMR coupling constants of the two methine protons in vicinally disubstituted lactones, which generally follow the trend $^{3}J_{cis}$ = 6.5 Hz > $^{3}J_{trans}$ = 4-4.5 Hz.[4] The inherent reactivity of this class of compounds stems from the high ring-strain (ca. 23 kcal/mol) of the four-membered heterocycle, and is akin to that of epoxides (ca. 27 kcal/mol).[5] This high ring-strain, together with the ambident electrophilicity of β-lactones (see Section 1.2.2), is the reason why this class of compounds is so useful and versatile.

1.2 Significance of β-Lactones

1.2.1 Motif in Drugs and Natural Products

Given the delicate balance of thermodynamic instability and kinetic inertness found in β-lactones, it would not come as a surprise if nature also took advantage of this functional moiety. Indeed, many natural products containing 2-oxetanones have been isolated and characterized over the years (Figure 1.1).[6] Just like their nitrogen-analogs, the β-lactams, β-lactones serve as potent electrophiles that can readily and irreversibly acylate critical functional groups in enzymes. Consequently, antibiotic behavior is often associated with such compounds.[7] Interestingly, the majority of these compounds feature vicinally or geminally disubstituted β-lactones.[6,8] This substitution pattern might serve as a means to regulate the inherent reactivity of these compounds until their deployment.

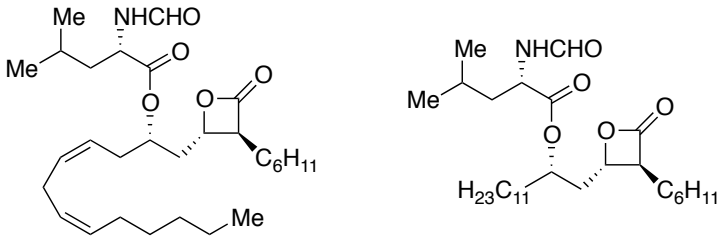


Spongiolactone (**1**) *Antibiotic 1233A* (**2**)

Ebelactone A (**3**) *Salinosporamide A* (**4**)

Figure 1.1 Selected natural products containing a β-lactone motif

At least one class of naturally occurring β-lactones has been developed further into an approved drug named Orlistat (Tetrahydrolipostatin (**6**), Figure 1.2). This drug is available over-the-counter in the US as a treatment for obesity, and operates by irreversibly deactivating lipases needed to digest triglycerides, thus interfering with the absorption of dietary fat in the gastrointestinal tract. Efforts to develop other kinds of drugs based on β-lactone motifs are currently underway.[9]

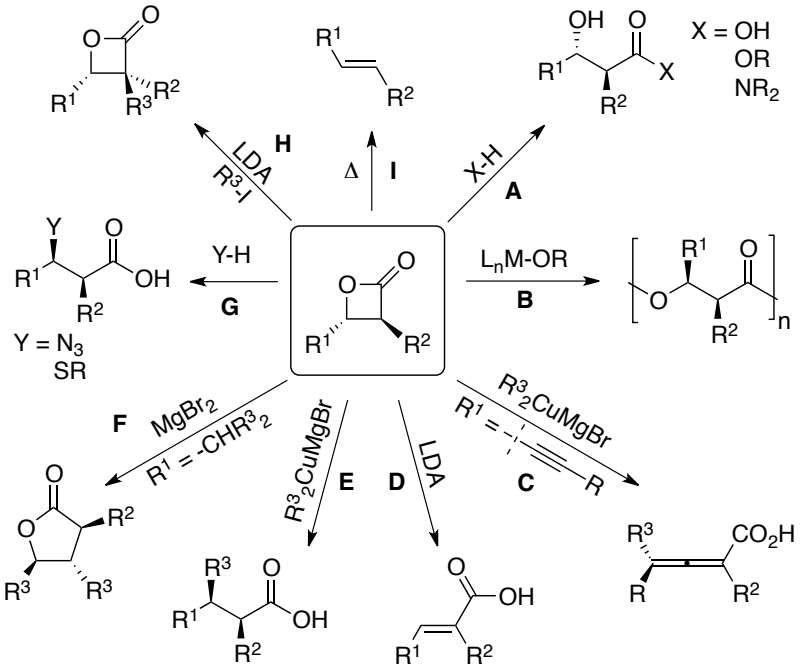


Lipstatin (**5**) *Tetrahydrolipstatin* (**6**)

Figure 1.2 The natural product Lipstatin (5) and its derivative Tetrahydro-lipstatin (6), an over-the-counter anti-obesity drug

1.2.2 Reactivity of β-Lactones

Due to the high innate reactivity of β-lactones, they can undergo a wide range of transformations as seen in Scheme 1.1.[3,10] Reaction with a variety of hard nucleophiles from groups 5 and 6 such as alcohols or amines generally leads to cleavage of the acyl-oxygen bond and gives rise to aldol-type carboxylic acids, esters, and amides (Scheme 1, route A). Given that these ring-opening reactions occur under relatively mild conditions with high conversions in a stereoselective manner, they represent a versatile and useful entry into stereopure aldol-products.[11] The reaction with alkoxides is of particular importance as it can produce polyesters (route B) in a controlled fashion, provided a suitable polymerization catalyst is available.[12,13]



Scheme 1.1 Selected transformations and products accessible from β-lactones

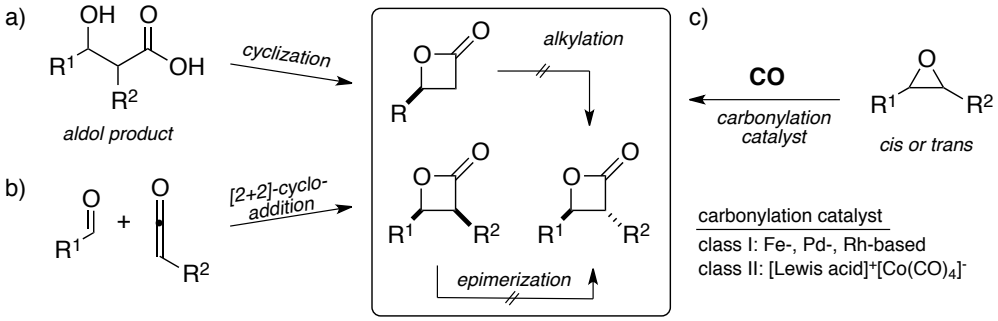
Thanks to the ambident electrophilicity of β-lactones, a second type of ring-opening reaction is also possible. For example, cleavage of the alkyl-oxygen bond is observed with soft nucleophiles such as thiols or azides.[11a] This mode of reactivity leads to β-azido- and β-thiocarboxylic acids under inversion of stereochemistry (route G). Additionally, cuprates of the type $R_2CuMgBr$ react in the very same way, thus allowing stereoselective introduction of an alkyl moiety in the β-position (route E).[11c] This transformation has also been applied to 4-alkynyl-2-oxetanones, which undergo a S_N2'-reaction, thus enabling stereoselective synthesis of highly substituted allenes (route C).[14] Other typical reactions of β-lactones include dyotropic rearrangements to γ-lactones (route F),[15] rearrangement to acrylate derivatives (route D),[16] stereo-selective decarboxylation to the corresponding alkene (route I),[17] and α-alkylation

(route H).[16,18] Overall, this versatility in reactivity is what makes β-lactones so interesting, and justifies further research endeavors aimed at their synthesis and usage.

1.3 Synthetic Routes to β-Lactones

1.3.1 Brief Survey of Common Approaches to β-Lactones

In light of the diverse set of reactions that β-lactones can undergo, it seems somewhat surprising that only two routes are routinely used for their synthesis (Scheme 1.2).[3] The first route consists of cyclization of an acyclic aldol-type precursor (Scheme 1.2a), and a variety of robust methods are available to carry out this approach either *in situ*[19] or with well-defined precursors.[20] Unfortunately, these routes often require several synthetic steps, and are not very economical because stoichiometric amounts of additional reagents are needed.



Scheme 1.2 Common synthetic approaches to mono- and disubstituted β-lactones

The second approach relies on catalyzed (formal) [2+2] cycloadditions of carbonyl compounds with ketenes (Scheme 1.2b).[21,22] If catalyzed, this route can give a wide range of β-lactones directly and often with good stereochemical control in the case of vicinally disubstituted β-lactones. On the downside, the required ketenes are

generally highly reactive compounds that need to be generated at low temperatures using basic conditions. Besides being inconvenient, this approach also introduces stoichiometric amounts of additional reagents. Moreover, the majority of these methods only produces mono- or *cis*-disubstituted β-lactones. On the other hand, the synthesis of *trans*-disubstituted β-lactones requires a special catalytic system (*vide infra*). At this point, it should also be noted that neither monosubstituted β-lactones nor *cis*-disubstituted β-lactones can easily be transformed into *trans*-disubstituted β-lactones via alkylation or epimerization, respectively.[18,23] Nevertheless, the [2+2]-cycloaddition approach has found wide acceptance in the synthetic community and has been applied to several total syntheses.[6a]

Ring-expansion carbonylation of epoxides (Scheme 1.2c) has recently emerged as a powerful, convenient, and direct method for the production of β-lactones, and has great potential to complement the aforementioned synthetic routes. Fundamentally, there are two different kinds of catalytic systems that can affect such transformations. The first class uses catalytic amounts of late-row transition metals such as rhodium, palladium, or stoichiometric amounts of iron carbonyls, and is limited to the carbonylation of alkenyl-substituted epoxides.[24] The second class consists of a Lewis acid paired with a metal carbonyl anion such as $[Co(CO)_4]^-$, and was found to be more applicable and versatile in terms of scope then the first class. [25,26] Consequently, the nuances of the second class will be discussed in more detail in the subsequent sections.

1.3.2 Epoxide Carbonylation Using Catalysts of the Form [Lewis acid]$^+$[Co(CO)$_4$]$^-$

In 2001, Alper and coworkers showed that epoxides can be carbonylated to the corresponding β-lactones by using a neutral Lewis acid in combination with a salt containing $[Co(CO)_4]^-$ as anion.[26a] Although this system was a major improvement over existing methods at that time, it still required high reaction temperatures together with long reaction times, and a limited substrate scope. Another major step forward was the introduction of catalytic systems based on frustrated ion pairs of the form [Lewis acid]$^+$[Co(CO)$_4$]$^-$ by Coates and coworkers in 2002.[26b,c] These systems were well defined, operated under milder conditions with a wide variety of epoxides, required only small catalyst loadings, and showed high chemoselectivity and

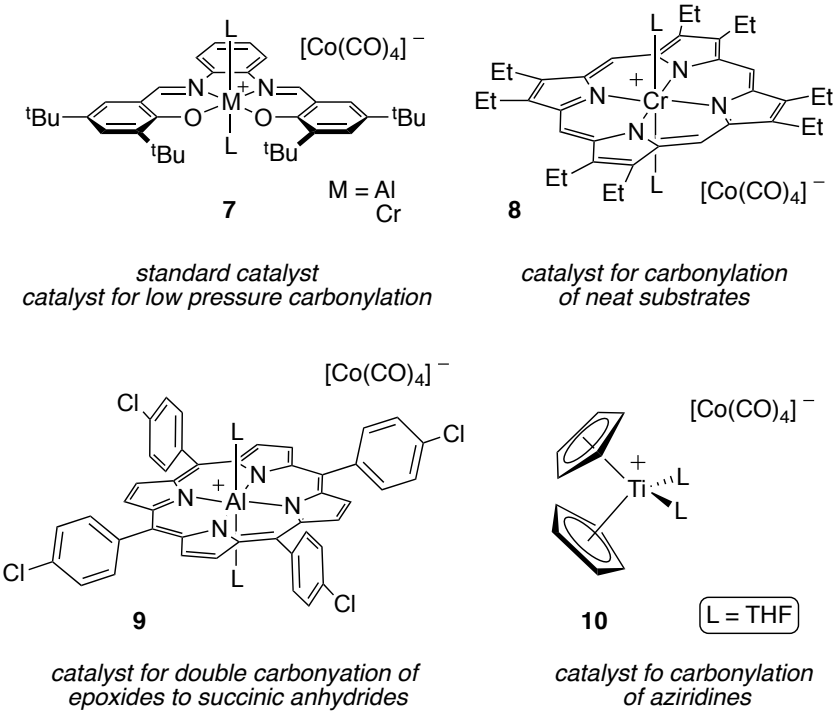
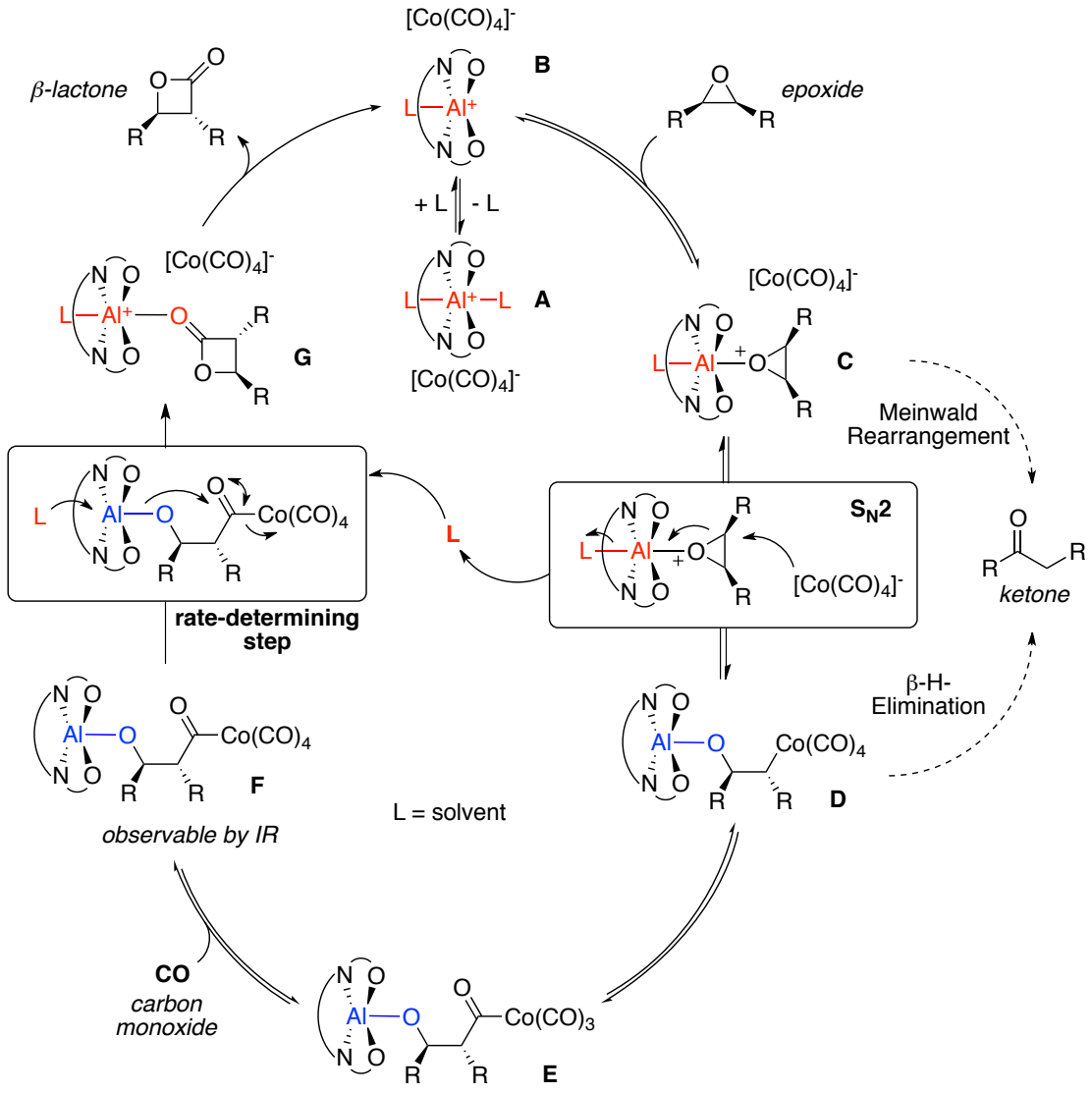


Figure 1.3 Selected carbonylation catalysts of the form [Lewis acid]$^+$[Co(CO)$_4$]$^-$ and their utility

functional group tolerance. Over the years, several generations of catalysts have been developed and optimized for different applications as can be seen in Figure 1.3.[26b-e,27]

Mechanistic investigations revealed an intricate interplay between the catalytic system, the epoxide substrate, and the reaction solvent, as well as the S_N2-mechanism by which the carbonylation reaction proceeds.[17,28,29] A general mechanism is shown in Scheme 1.3.[29]



Scheme 1.3 Proposed mechanism for carbonylation of epoxides using catalysts of the form [Lewis acid]$^+$[Co(CO)$_4$]$^-$

The postulated catalytic cycle shows that the isolated and characterized [Lewis acid]$^{+}$[Co(CO)$_4$]$^{-}$species (Scheme 1.3, **A**) is not the actual catalyst because the Lewis acid ions are coordinatively saturated by solvent molecules. This is also evident from X-ray analysis of single crystals. Consequently, the catalytically active species is formed initially *in situ* by loss of a molecule of solvent (**B**). The now unoccupied coordination site is then available for epoxide molecules. Upon coordination (**C**), the substrate becomes electrophilic enough so that the nucleophilic cobaltate-anion can perform a ring-opening reaction, which proceeds in an S_N2-type manner. Concomitant with this attack is the loss of another solvent molecule from the Lewis acidic metal. The newly formed cobalt species **D** then undergoes migratory insertion of a molecule of carbon monoxide into the cobalt-alkyl bond to give rise to **E**. In the next step, a molecule of CO is recruited from the surrounding solution to the cobalt-center, which subsequently produces the cobalt-acyl species **F**. This intermediate is observable by *in situ*-IR and was proposed to be the resting state of this catalytic cycle. In the following, rate-determining step, a solvent molecule recoordinates to the Lewis acidic metal, which initiates the ring-closing reaction of the organic substrate to the β-lactone product (**G**). Interactions like this between solvent molecules and catalyst rationalize the large solvent dependence of the reaction rate as well as product selectivity, for example mono- vs. biscarbonylation of epoxides.[27] Finally, the catalytically competent species **B** is reformed and ready to undergo another catalytic cycle.

Despite all the advantages that catalysts of the form [Lewis acid]$^{+}$[Co(CO)$_4$]$^{-}$ introduced to the field of ring-expansion carbonylation of epoxides, one component that is at the heart of synthesis still needs to be addressed further by these systems,

namely selectivity. Although carbonylation reactions proceed with high chemoselectivity (cf. Section 1.4.1) and follow a stereospecific mechanism, areas such as regioselectivity and enantioselectivity nonetheless remain challenging.

1.4 Selectivity in Epoxide Carbonylation Reactions Using [Lewis acid]$^+$[Co(CO)$_4$]$^-$ Catalysts: Opportunities and Challenges

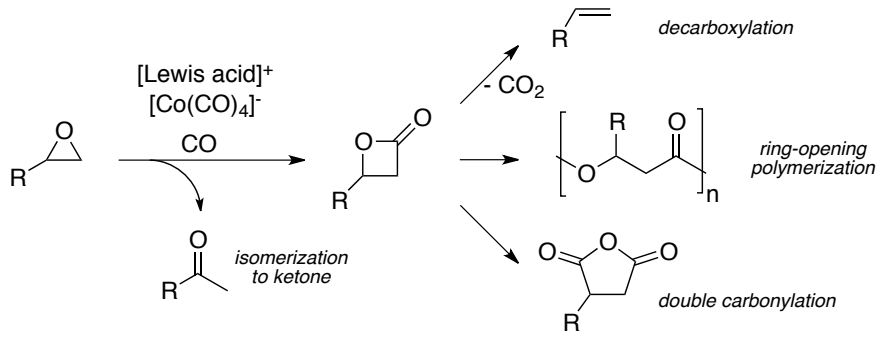
1.4.1 Chemoselectivity

As mentioned before, carbonylation of epoxides proceeds with such high chemoselectivity that upon completion of the reaction the β-lactone products can often be isolated via simple distillation. Scheme 1.3 indicates that the formation of ketone side products can become a problem at certain stages in the catalytic cycle.[25e] For example, upon coordination of the epoxide to the Lewis acid (Scheme 1.3, species **C**) the epoxide is activated enough do undergo a Meinwald rearrangement[30] to the corresponding ketone. Indeed, this reaction is observed exclusively in the presence of a non-nucleophilic anion such as tetraphenylborate. β-Hydride elimination from the intermediate cobalt-alkyl species **D** is another potential pathway to ketone formation, and can be suppressed by judicious choice of the Lewis acid or by applying pressures of CO exceeding 300 psi.[26e]

Other potential decomposition pathways for the β-lactone product under reaction conditions include ring-opening polymerization to polyesters, double carbonylation of the β-lactone to succinic anhydrides, or decarboxylation to the underlying alkene. The first two routes can be suppressed by the use of the right solvent, or even promoted if

so desired.[27,31] The degradation via decarboxylation is usually avoided by adjusting the reaction temperature accordingly.[32]

A summary of all potential degradation pathways discussed in this section is provided in Scheme 1.4.



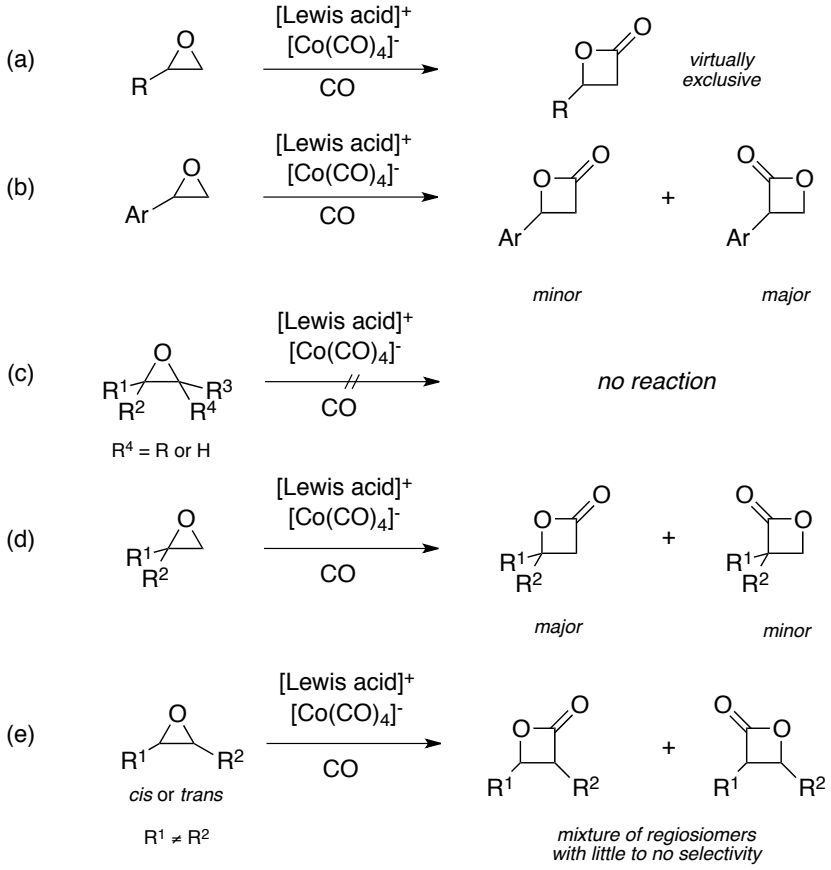
Scheme 1.4 Major pathways that can compromise the chemoselectivity of the ring-expansion carbonylation of epoxides to β-lactones

1.4.2 Regioselectivity

Terminal epoxides are carbonylated with excellent regioselectivities of >100 : 1 in favor of CO insertion at the methylene carbon (Scheme 1.5a). This steric preference is in line with what is expected from an S_N2-mechanism. The only exception is alkenyl-substituted epoxides such as styrene oxide, which show preferential incorporation of CO at the α- instead of the β-position (Scheme 1.5b).[33] Tri- and tetra-substituted epoxides, on the other hand, are inert to carbonylation reactions (Scheme 1.5c).[33]

A special scenario arises with 2,2'-disubstituted epoxides (Scheme 1.5d) Based on steric factors alone, one would expect exclusive carbonylation at the methylene carbon. However, the experimental observation is a mixture of both possible regioisomers.[26b,c] A possible explanation for this outcome lies in the very electrophilic nature of the Lewis acid ion. As the epoxide coordinates to the Lewis acid, it is

conceivable that a partial positive charge develops at the tertiary carbon of the epoxide. Even though orbital overlap favors attack at the methylene carbon, ionic interactions bias the attack of the cobalt-anion toward the tertiary carbon, which overall results in attack at both positions and yields the aforementioned mixture.



Scheme 1.5 Observed regioselectivies with literature-known carbonylation catalysts for selected types of epoxides

The most challenging substrates in terms of regiocontrol are unsymmetrically *cis*- or *trans*-disubstituted epoxides (Scheme 1.5e). This class of epoxides is particularly interesting because most known bioactive β-lactones consist of only a single *trans*-disubstituted regioisomer (cf. Section 1.2.1). Prior to the work presented in Chapter 2 in this thesis, only two examples regarding the carbonylation of this class of epoxides

were reported, and both proceeded with low regioselectivities.[33] Regioselective intermolecular reactions of unbiased *cis*- or *trans*-disubstituted epoxides that follow by an S_N2-mechanism are generally difficult to achieve with any sort of nucleophile.[34] Strategies to address this problem have been developed, and include a) use of epoxides that carry a strong electronic or steric bias,[35] b) utilization of a non-S_N2-mechanism for the ring-opening reaction,[36] c) restricting the reaction to an intramolecular event,[37] or d) use of a directing group present in the epoxide.[34b] While these methods can achieve very high regioselectivities, use of a selective catalyst that only temporarily alters the structure of the substrate while still achieving the same selectivity would be more desirable. Unfortunately, such catalytic systems are very rare.[38] As is often the case, nature has successfully taken on this problem and evolved enzymes called hydrolases that allow regioselective hydrolysis of vicinally disubstituted epoxides in mammalian cells.[39] However, to date no synthetic small molecule analog of these enzymes exists that shows good selectivity with a variety of *cis*- or *trans*-disubstituted epoxides. A potentially new design strategy for such catalysts is presented in Chapter 2, which addresses the problem of regioselective carbonylation of *cis*- or *trans*-disubstituted epoxides for a number of substrates.

1.4.3 Enantioselectivity

The enantioselective synthesis of β-lactones is of great importance given the wide range of products and reactions derived from them. The two aforementioned main synthetic routes to β-lactones, namely cyclization of aldol products and [2+2]-cycloadditions of ketenes with carbonyl compounds, can both be used to access

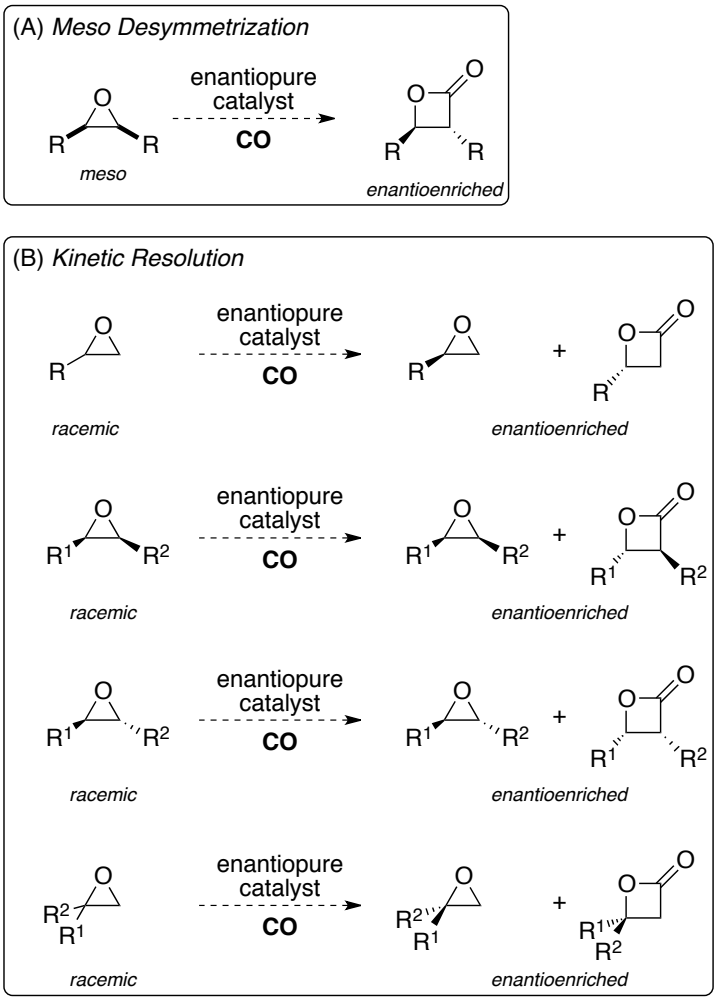
enantioenriched β-lactone products.[6a,10] As far as the cyclization route is concerned, many diastereo- and enantioselective (aldol) methodologies exist to synthesize the required precursors,[40,41] and some of these methods have been incorporated into powerful one-pot procedures.[42]

In addition to the cyclization route, enantioselective variants of the aforementioned [2+2]-cycloadditions exist, which rely on catalysis by either an enantiopure Lewis acid[10] or an enantiopure nucleophile.[43] While enantiopure Lewis acids afford only moderate enantioselectivities, enantiopure nucleophilic catalysts have been developed into a reliable and versatile synthetic tool for the synthesis of enantioenriched β-lactones.[44] Nonetheless, the aforementioned disadvantages associated with these methods still apply. Moreover, only mono- and *cis*-disubstituted β-lactone products are routinely accessible using the [2+2]-cycloaddition method. Direct *trans*-selective routes were unknown until recently,[45] and still require refinement.

Carbonylation of epoxides has the potential to be a very powerful approach to enantioenriched β-lactone products. Since stereochemistry is reliably transformed at the site of CO insertion during carbonylation reactions using [Lewis acid]$^+$[Co(CO)$_4$]$^-$-catalysts, enantioenriched epoxides are readily converted into the corresponding lactone products without erosion of enantiopurity.[26b] The required enantioenriched epoxides themselves can be accessed using a host of different methods.[46] Enantioenriched terminal epoxides are especially readily available thanks to techniques such as hydrolytic kinetic resolution.[46e] Overall, this combination of enantioselective epoxide synthesis and subsequent carbonylation reaction provides a

reliable two-step entry into enantioenriched β-lactone products. Alternatively, *racemic* β-lactones can be subjected to enzymatic kinetic resolution to obtain the same enantioenriched β-lactones.[47]

On the other hand, the synthesis of enantioenriched β-lactones starting directly from *meso* or *racemic* epoxides is significantly less advanced. Most of these routes would also have to rely on kinetic resolutions of epoxides (Scheme 1.6), yet no general synthetic method exists so far despite continuing efforts (see Chapter 3).[48] The



Scheme 1.6 Potential approaches to enantioenriched β-lactone products using enantiopure carbonylation catalysts

advantage of such methods over the use of already enantioenriched epoxide substrates would be that all of the epoxide substrate could eventually be transformed into β-lactone product using two rounds of carbonylation, instead of being forced to discard 50% of the epoxide in a resolution step prior to carbonylation. Furthermore, β-lactones derived from *meso* epoxides do not have an epoxide precursor that can be produced in an enantioenriched form. Consequently, enantioselective carbonylation catalysts are a must for this class of epoxides. Given the current dearth of such enantioselective carbonylation catalysts, this field still awaits further exploration.[49] New concepts on how this can potentially be achieved are presented in Chapter 3.

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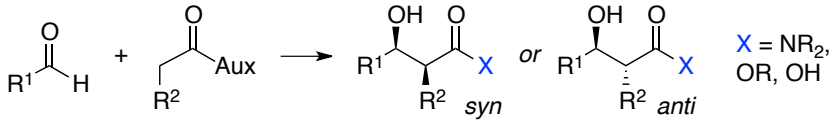
CHAPTER TWO

Development of New Catalyst Frameworks for the Regioselective Carbonylation of *cis*- and *trans*-Disubstituted Epoxides to β-Lactones

2.1 Introduction

The aldol reaction and its diverse array of products are of great importance in the synthesis of complex molecules and industrial processes.[1] Noteworthy features of this transformation are the formation of a C–C bond, and the concomitant creation of two contiguous stereocenters. Aldol products derived from so-called *propionate aldol reactions* (Figure 2.1, R^2 = Me) are of special interest,[2] and thus many excellent methods for their synthesis exist.[3]



- activating reagent in addition to catalyst / auxiliary (Aux) typically required
- strict control of reaction conditions often necessary
- challenge: control over diastereo- and enantioselectivity

Figure 2.1 Generalized (stereoselective) aldol reaction and common synthetic characteristics associated with it

A common deficiency of these methods, however, is the use of stoichiometric amounts of an activating agent, e.g. a base, to facilitate the reaction. Furthermore, strict control of reaction conditions and additional auxiliaries or catalysts are often needed to induce high levels of relative and absolute stereocontrol.[3] Taken together, these attributes can be disadvantageous in terms of cost and operational simplicity.

An alternative approach to the same line of aldol-type products utilizes α,β-disubstituted β-lactones. Due to their inherent reactivities, they can easily be converted into a wide variety of stereochemically well-defined aldol-type compounds, or rearranged to structures otherwise inaccessible *via* aldol reactions.[4,5] As mentioned before in Chapter 1, β-lactones also represent a valuable class of compounds due to

their occurrence in natural products,[6] and because of their ability to serve as monomers in the synthesis of polyesters.[7]

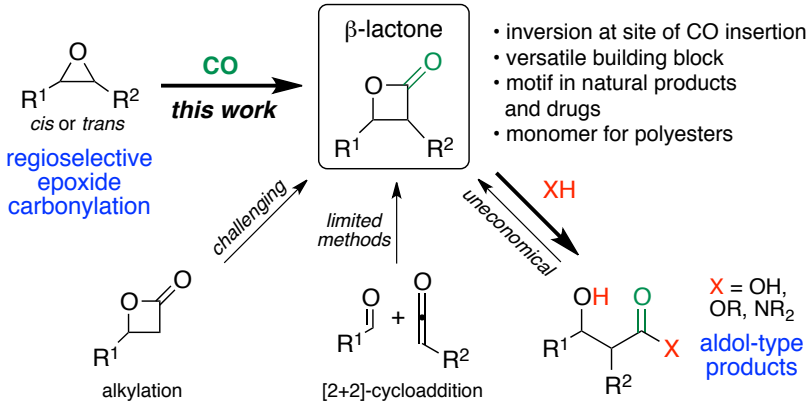


Figure 2.2 Common approaches to α,β-disubstituted β-lactones and regioselective epoxide carbonylation as a versatile alternative

Unfortunately, not many methods are currently available to make α,β-disubstituted β-lactones stereoselectively in a direct and economical fashion (Figure 2.2).[8] Of the methods available, most require lactonization of a corresponding acyclic precursor. However, these precursors themselves are typically derived from aldol reactions.[9] Another popular approach is the catalyzed (formal) [2+2]-cycloaddition of ketenes to carbonyl compounds. This transformation gives *cis*-β-lactones directly with often excellent stereoselectivity.[10] Drawbacks are the need to synthesize both reaction partners separately, the use of stoichiometric amounts of an activating agent, and careful control of the reaction parameters. Moreover, only a few catalytic systems are known to make *trans*-β-lactones by this method.[11]

Carbonylation of epoxides using catalysts of the form [Lewis acid]$^{+}$[Co(CO)$_4$]$^{-}$ has recently emerged as a reliable direct approach to β-lactones when using terminal or symmetrically *cis*- or *trans*-disubstituted epoxides as substrates.[12] Consequently,

this route seems like an attractive alternative method to obtain the aforementioned β-lactones and aldol-type products associated with them (Figure 2.3). The epoxide substrates are readily available in diastereo- and enantioenriched forms,[13] and the S_N2-mechanism of the carbonylation reaction transforms existing stereochemistry predictably.[14]

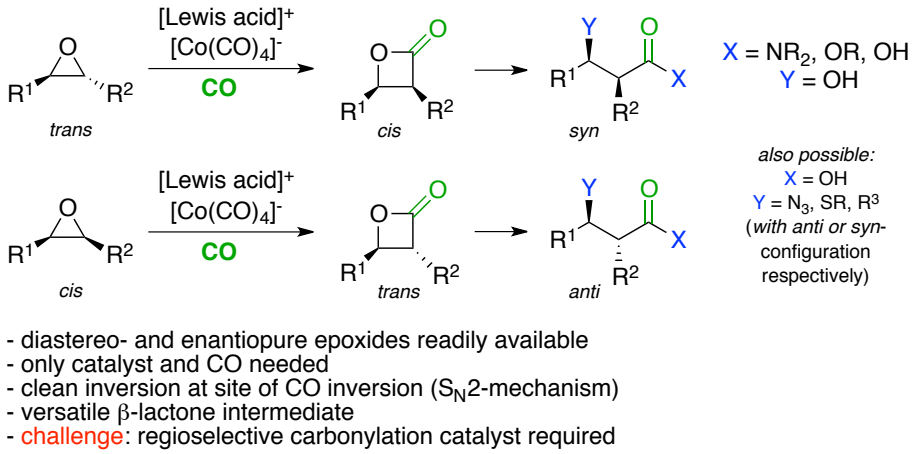
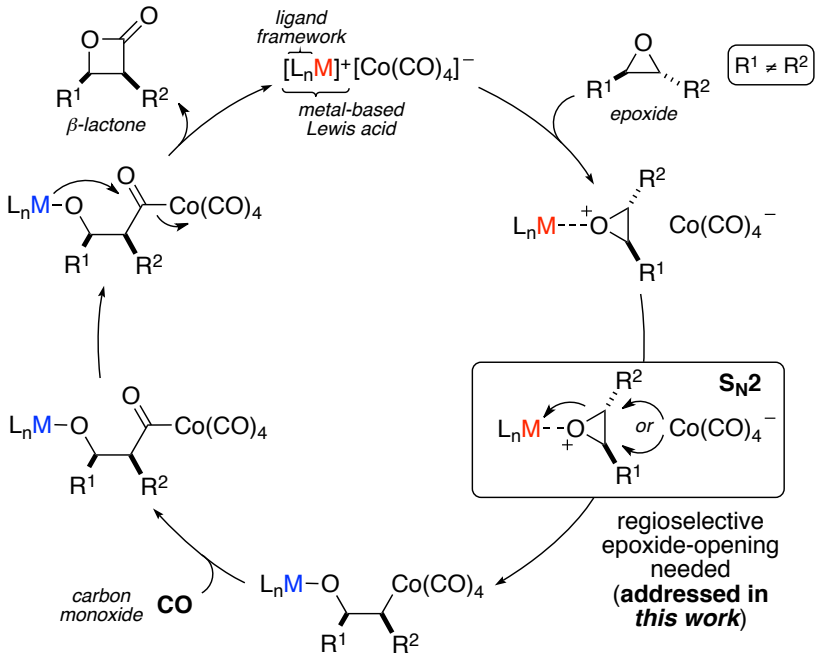


Figure 2.3 Regioselective epoxide carbonylation and subsequent β-lactone funtionalization as an alternative entry into aldol-type products

However, known carbonylation catalysts are prone to producing an unselective mixture of regioisomeric β-lactone products from *cis*- or *trans*-disubstituted epoxides. Presumably this is because of an unselective S_N2-ring opening reaction between the epoxide and the cobaltate anion in the case of electronically or sterically unbiased substrates (Scheme 2.1). Unselective S_N2-reactions are a general problem encountered with any nucleophile when trying to ring-open this class of epoxides.[15] Consequently, very few selective catalysts exist for such a reaction based on an S_N2-type mechanism.[16,17]

With the intent to address these problems, we report in the following four new salen-based catalysts that carbonylate *cis*- and *trans*-disubstituted epoxides with



Scheme 2.1 Simplified mechanism of epoxide carbonylation using [Lewis acid]$^+$ [Co(CO)$_4$]$^-$ catalysts, and the problem of regioselectivity

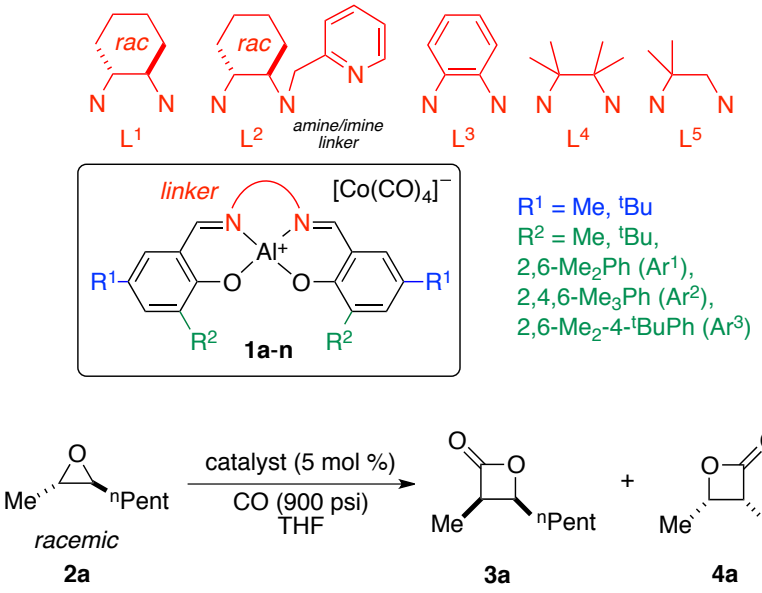
moderate to high regioselectivities. Each catalyst selectively produces a different isomer out of the four possible regioisomeric β-lactones. Use of these new catalysts consequently provides a convenient entry into a larger group of more complex α,β-disubstituted β-lactones and the aldol-type products associated with them starting from readily available epoxides. Given the large number of epoxide ring-opening reactions that are mediated by salen-type catalysts, these new systems could also be useful for applications beyond just carbonylation reactions. This idea is explored further by applying one of the new catalyst-frameworks to the regioselective transformation of vicinally disubstituted epoxides into chlorohydrins.

2.2 Regioselective Carbonylation of trans-Epoxides to cis-β-Lactones

2.2.1 Catalyst Development

Initial studies focused on identifying a ligand framework for the Lewis acidic metal ion that could impart high degrees of regioselectivity in the carbonylation of *trans*-epoxides (Table 2.1). Methyl-substituted epoxides such as **2a** were chosen as substrates because the resulting β-lactones **3a** and **4a** are both of interest. Lactone class **3** serves as a precursor for the aforementioned important propionate aldol products.[2] Lactones **4** give aldol-type products based on acetaldehyde, which can be a troublesome electrophile in aldol reactions due to its suspected carcinogenicity and propensity to hydrate or oligomerize. The salen-framework seemed to be a good starting point for ligand development because of its highly modular nature and known ability to form complexes that catalyze carbonylation reactions.[12,14] Previously reported salen-based carbonylation catalysts, however, showed poor activity at ambient temperature, and a modest contrasteric preference for β-lactone **4a** (entries 1-3). Consequently, a redesign of the ligand was necessary. Changing the ligand structure from the salen-type to a salalen-type (**L2**, catalyst **1e**) increased the preference for **4a** to more synthetically useful levels (entry 5). Use of a salalen-ligand also allowed for the incorporation of an additional pyridine donor ligand. Based on prior mechanistic studies,[14b] this was expected to facilitate the rate-determining step in the catalytic cycle, thus improving the low activity of catalysts such as **1a** at 22 °C. Indeed, complete conversion of epoxide **2a** and a slight increase in selectivity were observed with catalyst **1e** after solvent optimization (Table 2.2, entries 1-7).

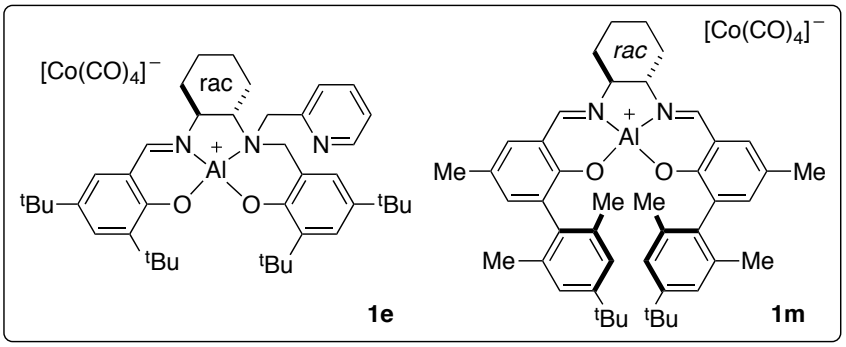
Table 2.1 Evaluation of carbonylation catalysts for the regioselective carbonylation of *trans*-epoxide 2a[a]

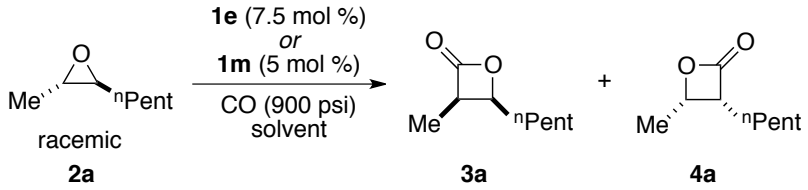


entry	linker	R^1	R^2	catalyst	ratio[b] **3a** : **4a**	conversion[b] (%)
1	L^1	^{t}Bu	^{t}Bu	**1a**	1 : 1.6	5
2	L^3	^{t}Bu	^{t}Bu	**1b**	1 : 1.6	12
3[c]	L^3	^{t}Bu	^{t}Bu	**1c**	1 : 1.2	10
4	L^4	^{t}Bu	^{t}Bu	**1d**	1 : 1.3	45
5	L^2	^{t}Bu	^{t}Bu	**1e**	1 : 3.7	41
6	L^1	Me	Me	**1f**	1.4 : 1	9
7	L^1	H	Ar^2	**1g**	n. d.	<5
8	L^1	Me	Ar^2	**1h**	10.1 : 1	40
9	L^3	Me	Ar^2	**1i**	11.5 : 1	23
10	L^4	Me	Ar^2	**1j**	2.3 : 1	87
11	L^5	Me	Ar^2	**1k**	6.7 : 1	71
12	L^1	Me	Ar^1	**1l**	11.5 : 1	40
13	L^1	Me	Ar^3	**1m**	11.5 : 1	>95
14	L^3	Me	Ar^3	**1n**	10.1 : 1	35

[a]Reaction conditions: [**2a**] = 0.5 M, 22 °C, 20 h. With the exception of **1a-e**, catalysts were generated *in situ* (L_nAlCl + $NaCo(CO)_4$). [b]As determined by ^{1}H NMR/GC analysis from crude reaction mixture. [c]Use of Cr^{3+} instead of Al^{3+} as Lewis acidic metal ion. [d]7.5 mol % **1e** used. n. d. = not determined.

Table 2.2 Evaluation of solvents in the regioselective carbonylation of *trans*-epoxide 2a using optimized catalysts 1e and 1m[a]





entry	solvent	catalyst	ratio[b] **3a** : **4a**	conversion[b] (%)
1	THF	**1e**	1 : 3.7	41
2	1,4-dioxane	**1e**	1 : 4.0	2
3	toluene	**1e**	1 : 4.0	71
4	benzene	**1e**	1 : 4.0	>95
5	xylenes	**1e**	1 : 4.2	21
6	anisole	**1e**	1 : 4.0	48
7	hexanes	**1e**	1 : 4.2	60
8	THF	**1m**	11.5 : 1	>95
9	1,4-dioxane	**1m**	10.6 : 1	81
10	toluene	**1m**	6.9 : 1	24[c]
11	DME	**1m**	10.6 : 1	>95
12	THP	**1m**	9.4 : 1	25

[a]Reaction conditions: [**2a**] = 0.5 M, 22 °C, 12 h. Catalyst **1m** was generated *in situ* (L_nAlCl + $NaCo(CO)_4$). [b]As determined by ^1H NMR/GC analysis from crude reaction mixture. [c]Significant amounts of ketone as by-product detected.

Catalyst **1e** proved useful for the enhanced production of **4a**, yet a carbonylation catalyst that would strongly favor formation of regioisomer **3a** was still more

desirable. A first indication how this could be achieved came in the form of catalyst **1f** (Table 2.1, entry 6). The small size of the substituents R^1 and R^2 in this catalyst gave rise to a small shift in selectivity toward **3a**. A subsequent adjustment of the steric hindrance in R^2 then gave rise to very good selectivity, yet catalyst activity was still only moderate (entry 8). Variation of the diamine-linker yielded unsatisfactory results (entries 9-11). However, fine-tuning the steric size of the aryl-group in R^2 (entries 12 and 13) led to catalyst **1m**, which in THF showed the best activity and selectivity in producing **3a** (Table 2.2, entries 8-12).

To date, only low quality X-ray crystals of **1m** could be obtained (Figure 2.4, R = 0.0707, $wR2$ = 0.1832). Nonetheless, their analysis indicates that the ligand coordinates in the salen-typical *trans*-planar geometry around the Al^{3+}-ion, albeit in a rather distorted fashion.[18]

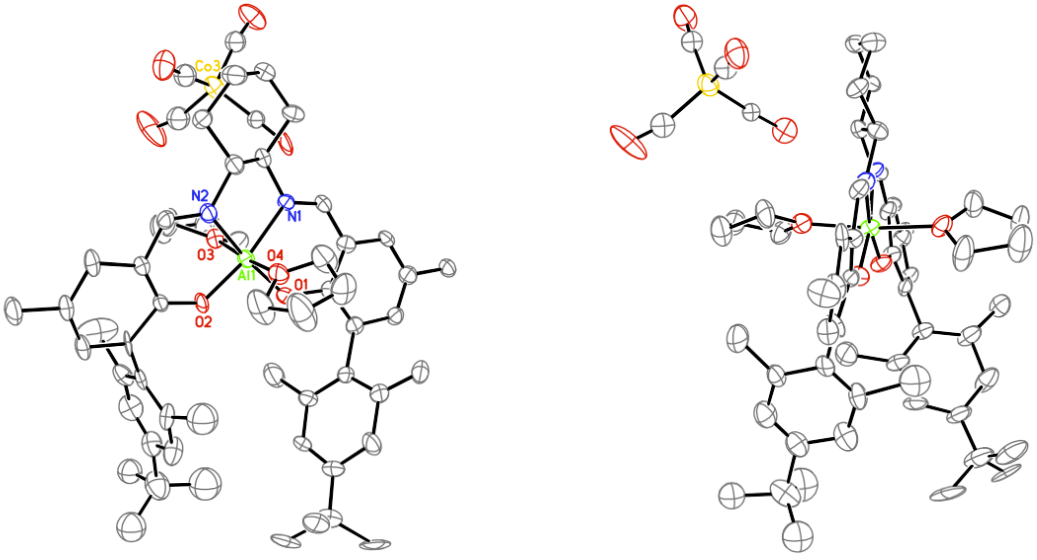
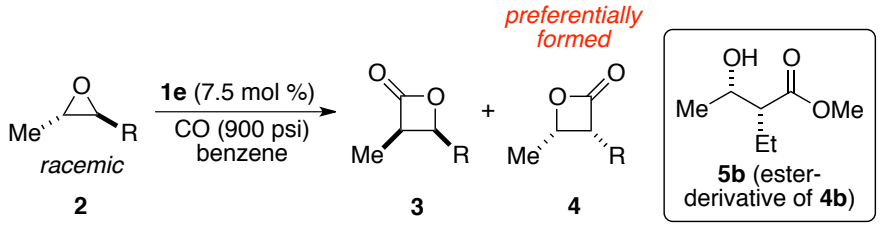


Figure 2.4 Low quality crystal data for catalyst 1m

2.2.2 Scope of the Regioselective Carbonylation Using Catalysts 1e and 1m

Catalysts **1e** and **1m** were subsequently tested for the regioselective carbonylation of a variety of *trans*-disubstituted epoxides **2** (Table 2.3 and Table 2.4). GC or ^{1}H NMR analysis of crude reaction mixtures indicated full conversion of starting material to lactone with both catalysts in almost all cases. The resulting regioisomeric β-lactone products **3** and **4** could be separated from one another either directly *via* column chromatography, or after converting them into the corresponding ester-derivatives **5** and **6** using a one-pot sequence by quenching the reaction with MeOH/NaOMe. The latter approach showcases how the obtained β-lactones can readily be converted into related aldol moieties with well-defined stereochemistry.

Table 2.3 Regioselective carbonylation of *trans*-disubstituted epoxides to β-lactones using catalyst 1e[a]



entry	R (**epoxide**)	ratio[b] **3** : **4**	isolated product	isolated yield (%)
1[c]	Et (**2b**)	1 : 3.0	**5b**	63
2	^{n}Pr (**2c**)	1 : 3.7	**4c**	60
3[c]	^{n}Bu (**2d**)	1 : 3.5	**4d**	65
4	^{n}Pent (**2a**)	1 : 4.0	**4a**	68
5	^{n}Hex (**2e**)	1 : 4.6	**4e**	71
6	$(CH_2)_3$OTBS (**2f**)	n. d.	**4f**	<5[b]

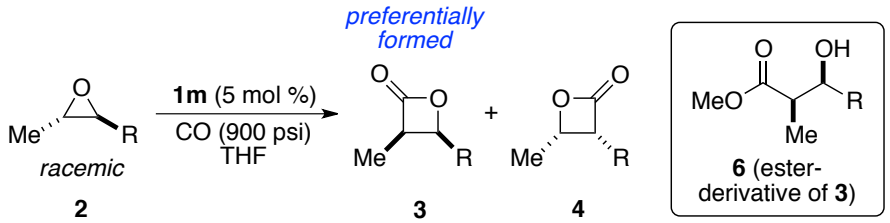
[a]Reaction conditions: [**2**] = 0.5 M, 22 °C, 22 h. All reactions gave full conversion (GC or ^{1}H NMR analysis), except for **2f** (<5%). Yields refer to isolated products. [b]Determined by ^{1}H NMR analysis of crude reaction mixture. [c]5 mol % of **1e** used. n. d. = not determined. TBS = ^{t}BuMe$_2$Si.

Carbonylation of *trans*-epoxides **2** with catalyst **1e** gave good preference for β-lactones **4** (Table 2.3), with ratios **3** : **4** falling in the range from 1 : 3.0 to 1 : 4.6. Interestingly, **1e** displayed an almost steady increase in regioselectivity for epoxides **2a**-**e** (entries 1-5). This seems counterintuitive because longer alkyl-chains should shield their side of the epoxide more from nucleophilic attacks than shorter ones. In line with this expectation, epoxides with sterically more demanding substituents R such as **2f** gave no formation of any lactone when exposed to **1e** (entry 6). Nevertheless, the contrasteric selectivities achieved with **1e** are without precedence for this group of epoxides, and cannot readily be explained by invoking an inherent steric or electronic bias.

In comparison to **1e**, catalyst **1m** generally showed higher regioselectivities in the carbonylation of *trans*-epoxides **2**, with ratios **3** : **4** typically exceeding 10.0 : 1 in favor of **3** (Table 2.4). Only epoxide **2b** gave a lower ratio of 6.1 : 1 (entry 1). Given the similarity of the epoxide substituents in **2b** (Me vs. Et), this is still a very good ratio, and underscores the ability of **1m** to effectively enhance even small degrees of steric bias contained in **2**. In contrast to the trend observed with **1e**, epoxides **2a**,**c**-**e** showed little variation in regioselectivity as the length of the alkyl-chain was altered (entries 2-5). As expected, *trans*-epoxides **2** with sterically more demanding substituents R gave even better selectivities toward β-lactones **3** (entries 6-9). In case of **2h** and **i**, this additional bias was strong enough to form lactones **3h** and **i** almost exclusively, with only trace amounts of **4h** and **i** being detectable *via* ^{1}H NMR spectroscopy. However, placement of steric bulk immediately adjacent to the epoxy-group (**2j**, entry 10) gave a mixture of **3** and **4** and relatively poor conversion.

Likewise, *trans*-epoxides with sterically very similar substituents gave rather low selectivities when using catalyst **1m**. For example, *trans*-2-butyl-3-ethyloxirane (**2k**) gave a ratio of 2.7 : 1 of regioisomeric β-lactones, and 25% conversion with **1m** under standard reaction conditions (^{1}H NMR analysis).

Table 2.4 Regioselective carbonylation of *trans*-disubstituted epoxides to β-lactones using catalyst 1m[a]



entry	R (**epoxide**)	ratio[b] **3** : **4**	isolated product	isolated yield (%)
1	Et (**2b**)	6.1 : 1	**6b**	60
2	^{n}Pr (**2c**)	11.5 : 1	**6c**	68
3	^{n}Bu(**2d**)	13.3 : 1	**6d**	74
4	^{n}Pent (**2a**)	11.5 : 1	**6a**	79
5	^{n}Hex (**2e**)	13.3 : 1	**6e**	85
6	$(CH_2)_3$OTBS (**2f**)	19.0 : 1	**6f**	75
7[c]	$(CH_2)_2$OTBS (**2g**)	24.0 : 1	**6g**	81
8[d]	CH_2OTBS (**2h**)	>50 : 1	**3h**	92
9	CH_2Ph (**2i**)	>50 : 1	**3i**	84
10	^{i}Pr (**2j**)	10.1 : 1	**3j** + **4j**[b]	45[b]

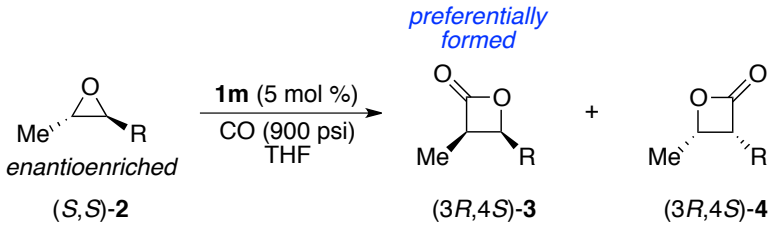
[a]Reaction conditions: [**2**] = 0.5 M, 22 °C, 20 h. All reactions gave full conversion (GC or ^{1}H NMR analysis), except for **2j** (45%). Yields refer to isolated products. [b]Determined by ^{1}H NMR analysis of crude reaction mixture. [c]7.5 mol % **1m** used. [d]10 mol % **1m** used. TBS = ^{t}BuMe$_2$Si.

2.2.3 Regioselective Carbonylation of Enantiopure Epoxides using Catalyst 1m

Given the good performance of **1m**, its ability to regioselectively carbonylate enantioenriched *trans*-epoxides was investigated next. The use of enantioenriched epoxides is very attractive because several excellent methods for their preparation exist,[13] and stereochemistry is reliably converted during carbonylation reactions.[14] A potential pitfall, however, lies in the fact that **1m** is typically used as a racemate. This can lead to matched/mismatched combinations[19] between the enantioenriched epoxide and the two enantiomers of the *racemic* catalyst, thus potentially diminishing the good selectivities observed before with *racemic* epoxides. To explore this scenario, highly enantioenriched (*S*,*S*)-**2e** (>95% ee) and (*S*,*S*)-**2i** (99% ee) were synthesized and carbonylated using *racemic* versions of **1m** (Table 2.5).

The good regioselectivities and activities were retained with both enantioenriched epoxides when using *rac*-**1m** (entries 1-2, and 5-6). These results indicate that **1m** is well suited for the regioselective carbonylation of enantioenriched *trans*-epoxides, which ultimately leads to enantioenriched aldol-type products. The use of enantiopure catalyst also allowed for the identification of matched/mismatched-pairs between the epoxide and the carbonylation catalyst. As Table 2.5 shows, *trans*-epoxides with (*S*,*S*)-configuration constitute a mismatched pair with (*S*,*S*)-**1m**, leading to significantly reduced selectivity and activity (entries 3 and 7). The matched case with (*R*,*R*)-**1m**, however, improves further on the already good selectivity and produced the preferred regioisomer **3** almost exclusively (entries 4 and 8).

Table 2.5 Regioselective carbonylation of enantioenriched *trans*-disubstituted epoxides (*S*,*S*)-2e and i using catalyst 1m[a]



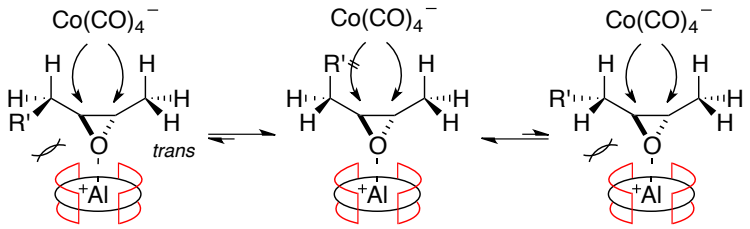
entry	R (**epoxide**)	catalyst	ratio[b] **3** : **4**	conversion[b] (%)
1	^{n}Hex (*rac*-**2e**)	*rac*-**1m**	13.3 : 1	>95
2	^{n}Hex (*S*,*S*-**2e**)	*rac*-**1m**	13.3 : 1	>95
3	^{n}Hex (*S*,*S*-**2e**)	(*S*,*S*)-**1m**	1.6 : 1	80
4	^{n}Hex (*S*,*S*-**2e**)	(*R*,*R*)-**1m**	32.3 : 1	>95
5	CH_2Ph (*rac*-**2i**)	*rac*-**1m**	>50 : 1	>95
6	CH_2Ph (*S*,*S*-**2i**)	*rac*-**1m**	>50 : 1	>95
7	CH_2Ph (*S*,*S*-**2i**)	(*S*,*S*)-**1m**	13.4 : 1	56
8	CH_2Ph (*S*,*S*-**2i**)	(*R*,*R*)-**1m**	>50 : 1	>95

[a]Reaction conditions: [**2**] = 0.5 M, 22 °C, 20 h. [b]Conversion to lactone, determined by ^{1}H NMR analysis of crude reaction mixture.

It is currently unclear, why (*R*,*R*)-**1m** preferentially interacts with (*S*,*S*)- instead of (*R*,*R*)-*trans*-epoxides **2**, and how the catalyst is able to induce such high levels of regioselectivity. Steric interactions presumably play a major role in both processes. Moreover, it is reasonable to assume that binding of epoxide **2** to the sterically encumbered Lewis acid restricts the number of conformations that its substituent R can adopt (Figure 2.5a). Similar levels of conformational restriction are probably absent when less sterically bulky Lewis acids are used (Figure 2.5b). The effect of such restrictions would then be that substituent R is confined to conformations that

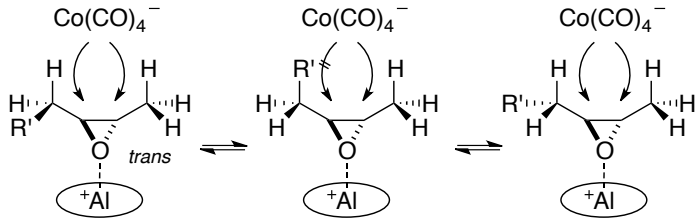
shield its corresponding epoxy-methine-carbon from nucleophilic attacks, thus strongly favoring ring opening of the epoxide at the observed position.

a) Proposed interaction of bound *trans*-disubstituted epoxide with carbonylation catalysts based on Lewis acids with sterically encumbered salen-ligands



major epoxide conformation → regioselectivity

b) Proposed interaction of bound *trans*-disubstituted epoxide with carbonylation catalysts based on Lewis acids with "flat" salen-ligands



no major epoxide conformation → little regioselectivity

Figure 2.5 Proposed effect of salen-ligand framework on epoxide conformation and resulting regioselectivity

2.2.4 Conclusion

In summary, two new carbonylation catalysts **1e** and **1m** are reported that convert *trans*-disubstituted epoxides **2** into the corresponding regioisomeric β-lactones **3** and **4**. Due to the excellent regioselectivities displayed by **1e** and **1m**, only one of the two β-lactone regioisomers is predominantly produced in these reactions. Moreover, the two catalysts show opposing regioselectivities, and thus provide access to a large variety of α,β-disubstituted β-lactones starting from readily available epoxides and carbon monoxide. In addition, these features are retained with enantiopure epoxides, and regioselectivity can be improved even further by matching enantiomers of catalyst and epoxide.

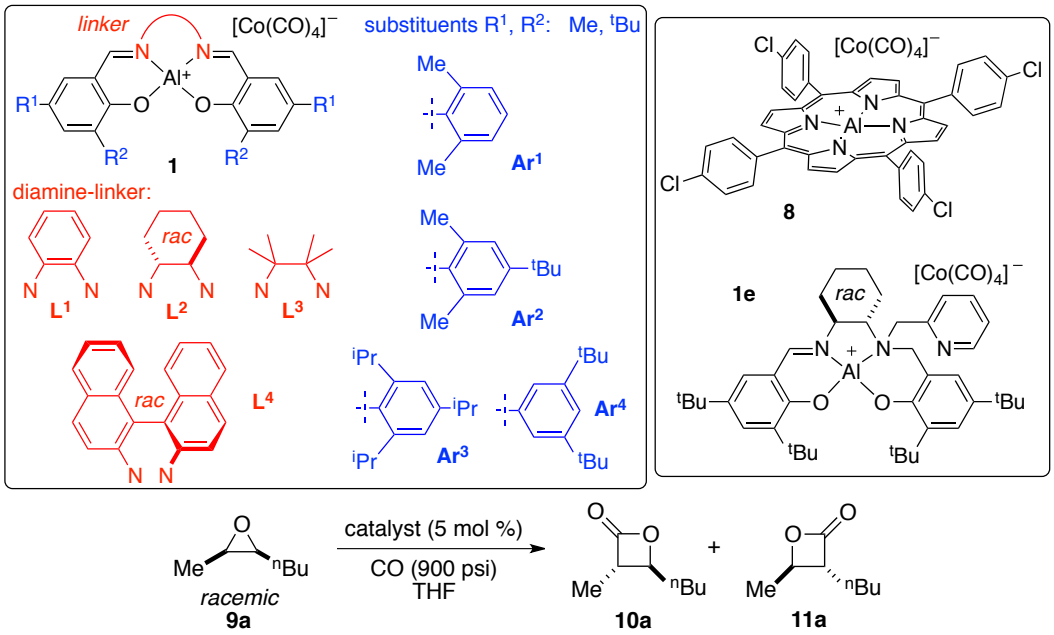
2.3 Regioselective Carbonylation of cis-Epoxides to trans-β-Lactones

2.3.1 Catalyst Development

A great number of naturally occurring β-lactones are α,β-disubstituted, exist as a single regioisomer, and display *trans*-configuration.[20] Consequently, carbonylation of *cis*-disubstituted epoxides would be of great value if it could be performed in such a way that the resulting *trans*-configured β-lactones where produced with high regioselectivity. Unfortunately, the catalysts introduced for the regioselective carbonylation of *trans*-epoxides, **1e** and **1m**, gave unsatisfactory selectivities with *cis*-disubstituted epoxides such as **9a** (Table 2.6, entries 1 and 2). As a result, two additional catalysts had to be found that show high activities and opposing regioselectivities for the carbonylation of *cis*-disubstituted epoxides to the corresponding *trans*-β-lactones.

Given the success of salen-based ligands in the regioselective carbonylation of *trans*-epoxides, we felt confident that analogous frameworks could also yield highly active and selective catalysts for *cis*-epoxides. Consequently, a variety of salen based-carbonylation catalysts were screened for the selective synthesis of regioisomer **10a** starting from *cis*-epoxide **9a** (Table 2.6). The resulting β-lactones **10** would give rise to potentially useful propionate aldol-type motifs commonly found in natural products synthesis.[2] Test reactions using literature-known catalysts **1a-c** already yielded good conversions and selectivities for lactone **10a** (entries 3-5). Interestingly, the use of chromium as Lewis acidic metal ion produced a more active yet less selective catalyst in comparison to the aluminum-based systems, and thus was not pursued further.

Table 2.6 Evaluation of carbonylation catalysts for the regioselective carbonylation of *cis*-disubstituted epoxides to *trans*-β-lactones[a]



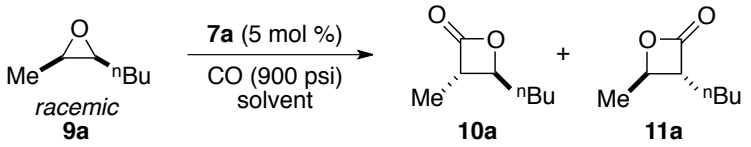
entry	Linker	R^1	R^2	catalyst	ratio[b] **10a** : **11a**	conv.[b] (%)
1	-	^{t}Bu	^{t}Bu	**1e**	1 : 1.3	>95
2	L^2	Me	Ar^2	**1m**	3.0 : 1	72[c]
3[d]	L^1	^{t}Bu	^{t}Bu	**1c**	2.1 : 1	95
4	L^1	^{t}Bu	^{t}Bu	**1b**	3.0 : 1	74
5	L^2	^{t}Bu	^{t}Bu	**1a**	2.7 : 1	72
6	L^3	^{t}Bu	^{t}Bu	**1d**	3.3 : 1	>95
7	L^3	^{t}Bu	Me	**1o**	2.0 : 1	>95
8	L^3	Me	Me	**1p**	2.1 : 1	>95
9	L^3	Me	H	**1q**	2.1 : 1	>95
10	L^3	Ar^3	^{t}Bu	**1r**	2.1 : 1	>95
11	L^2	Me	Ar^1	**1l**	1.6 : 1	74
12	L^4	Me	Ar^4	**7a**	1 : 11.5	63
13[e]	-	-	-	**8**	2.9 : 1	>95

[a]Reaction conditions: [**9a**] = 0.5 M, 22 °C, 20 h. [b]Conversion to lactone and ratio of regioisomers determined by GC or ^{1}H NMR analysis of crude reaction mixture. [c]The remainder was 3-heptanone. [d]Cr^{3+} used as Lewis acidic metal ion. [e]2 mol % of **8** used All catalysts except **1d**,**e**,**m** and **8** were prepared *in situ* ($L_nAlCl + NaCo(CO)_4$).

Changing the diamine-linker to 2,3-dimethylbutane-2,3-diamine (**L3**) preserved the good regioselectivity observed with linkers **L1** and **L2**, and further increased the activity of the catalytic system (entry 6). Variation of the steric size of substituents R^1 and R^2 had no beneficial effect in terms of selectivity (entries 7-10), consequently **1d** was the catalyst of choice (Figure 2.6).

When testing catalysts akin to **1l** and **1m** that featured 1,1'-binaphtyl-2,2'-diamine (DABN) as the diamine-linker, a reversal in regioselectivity in favor of lactone **11a** was noted. Use of this moiety together with 3,5-^{t}Bu-phenyl as substituent R^2 then gave rise to catalyst **7a** (entry 12), which displayed excellent contrasteric regioselectivity. Use of 1,4-dioxane instead of THF as solvent enhanced the selectivity for lactone **11a** even further (Table 2.7).

Table 2.7 Evaluation of solvents in the regioselective carbonylation of *cis*-epoxide 9a using catalyst 7a[a]



entry	solvent	ratio[b] **10a** : **11a**	conv.[b] (%)
1	THF	1 : 11.5	63
2	1,4-dioxane	1 : 24.0	>95
3	THP	1 : 10.1	41
4	Et_2O	1 : 7.3	>95

[a]Reaction conditions: [**9a**] = 0.5 M, 22 °C, 20 h. [b]Conversion to lactone and ratio of regioisomers determined by GC or ^{1}H NMR analysis of crude reaction mixture. Catalyst **7a** prepared *in situ* (L_nAlCl + $NaCo(CO)_4$).

With two competent and complementary carbonylation catalysts in hand (Figure 2.6), the scope of each catalytic system was investigated.

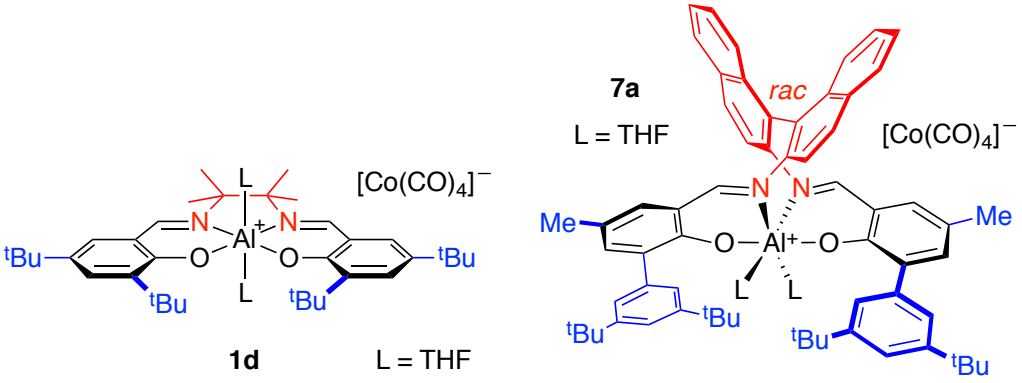
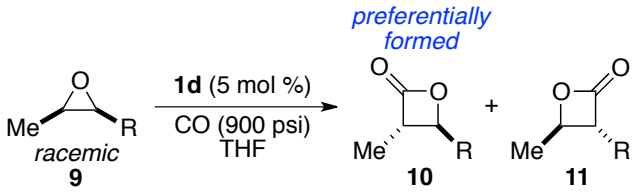


Figure 2.6 Optimized catalysts 1d and 7a for the regioselective carbonylation of *cis*-disubstituted epoxides

2.3.2 Scope of the Regioselective Carbonylation Using Catalysts 1d and 7a

Cis-epoxides **9** typically gave synthetically useful regioselectivities of greater than 3.0 : 1 in favor of lactones **10** when using catalyst **1d** (Table 2.8). It is worth noting that epoxides **9** with linear alkyl chains as substituent R showed good selectivities in the range of 2.9 to 3.8 : 1 irrespective of the length of the alkyl chain (entries 1-5). In the case of epoxides with sterically more demanding substituents R,

Table 2.8 Regioselective carbonylation of *cis*-disubstituted-epoxides 9 yielding β-lactones 10 using catalyst 1d[a]



entry	R (**epoxide**)	ratio[b] **10** : **11**	isol. product	isol. yield (%)
1	Et (**9b**)	3.2 : 1	**10b** + **11b**	66
2[c]	^{n}Pr (**9c**)	2.9 : 1	**10c** + **11c**	62
3	^{n}Bu (**9a**)	3.3 : 1	**10a** + **11a**	80
4	^{n}Pent (**9d**)	3.8 : 1	**10d** + **11d**	74
5	^{n}Hex (**9e**)	3.5 : 1	**10e** + **11e**	91
6	CH_2Cy (**9f**)	5.7 : 1	**10f** + **11f**	88
7[c]	CH_2Ph (**9g**)	19.0 : 1	**10g** + **11g**	90
8[c]	$(CH_2)_2Ph$ (**9h**)	3.5 : 1	**10h** + **11h**	86
9	$(CH_2)_2{}^{i}Pr$ (**9i**)	3.3 : 1	**10i** + **11i**	90
10[c]	$(CH_2)_2OTBS$ (**9j**)	4.0 : 1	**10j** + **11j**	87
11	$(CH_2)_3OTBS$ (**9k**)	2.7 : 1	**10k** + **11k**	92

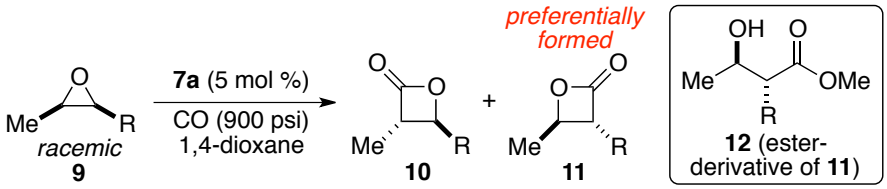
[a]Reaction conditions: [**9**] = 0.5 M, 22 °C, 20 h. All reactions gave full conversion (GC or ^{1}H NMR analysis). [b]As determined by ^{1}H NMR analysis of crude reaction mixture. [c]7.5 mol % of **1d** used. TBS = $^{t}BuMe_2Si$.

one would predict an increase in selectivity due to a stronger inherent steric bias. Indeed, such additional bias benefited selectivity as long as it was situated close to the epoxide (entries 6 and 7). Distancing it further away, however, made it ineffective quickly (entries 8-11), and the obtained selectivities resembled those achieved with epoxides **9a-e**. Interestingly, epoxides **9f** and **9g** gave very different ratios of **10** and **11** despite their structural similarity.

The two resulting lactones **10** and **11** could generally not be separated quantitatively from one another using column chromatography. Therefore, a mixture of the two lactones was isolated in all cases in yields usually exceeding 80%. The somewhat lower yields in entries 1 and 2 can be attributed to the volatility of the lactone products. It should be noted that ring-opening of **10** and **11** to the corresponding aldol-type methyl-esters by quenching the reaction with MeOH/NaOMe allowed for facile separation of the two regioisomers as is shown for catalyst **7a** in the following Table 2.9.

Selective formation of lactones **11** using catalyst **7a** proceeded extremely well, with ratios in favor of **11** exceeding 10.0 : 1 for nearly all *cis*-epoxides **9** tested (Table 2.9). Even the simple *cis*-epoxide **9b** gave a very good selectivity of 10.1 : 1 (entry 1), and better ratios were achieved for epoxides with longer alkyl-chains (entries 2-5). Similar to **1d**, catalyst **7a** did not show much variance in selectivity as the length of the linear alkyl-chain in substituent R was altered, the only exception being **9b**. It is also worth noting that *racemic* **7a** carbonylated enantioenriched epoxides such as (2*R*,3*S*)-heptene oxide ((2*R*,3*S*)-**9a**) with regioselectivities similar to those obtained

Table 2.9 Regioselective carbonylation of *cis*-disubstituted epoxides yielding β-lactones 11 and methyl-esters 12 using catalyst 7a[a]



entry	R (**epoxide**)	ratio[b] **10** : **11**	isol. product	isol. yield (%)
1	Et (**9b**)	1 : 10.1	**12b**	70
2	^{n}Pr (**9c**)	1 : 15.7	**12c**	77
3	^{n}Bu (**9a**)	1 : 24.0	**10a** + **11a**	69
4	^{n}Pent (**9d**)	1 : 24.0	**10d** + **11d**	74
5	^{n}Hex (**9a**)	1 : 19.0	**10e** + **11e**	72
6[c]	^{n}Bu (2*R*,3*S*-**9a**)	1 : 24.0	**10a** + **11a**	>95[d]
7	CH_2Cy (**9f**)	1 : 4.9	**10f** + **11f**	83[d]
8	CH_2Ph (**9g**)	1 : 1.3	**10g** + **11g**	18[d]
9	$(CH_2)_2Ph$ (**9h**)	1 : 32.3	**12h**	83
10	$(CH_2)_2{}^{i}Pr$ (**9i**)	1 : 19.0	**12i**	78
11	$(CH_2)_2OTBS$ (**9j**)	1 : 24.0	**12j**	81
12	$(CH_2)_3OTBS$ (**9k**)	1 : 13.3	**12k**	80
13	$(CH_2)_3OAc$ (**9l**)	1 : 10.1	**10l** + **11l**	82

[a]Reaction conditions: [**9**] = 0.5 M, 22 °C, 20 h. All reactions gave full conversion (GC or ^{1}H NMR analysis), except for **9f** and **9g**. [b]As determined by ^{1}H NMR analysis of crude reaction mixture. [c](2*R*,3*S*)-heptene oxide (99% ee) was used. [d]% Conversion to β-lactone (^{1}H NMR analysis). Catalyst **7a** prepared *in situ* ($L_nAlCl + NaCo(CO)_4$). TBS = $^{t}BuMe_2Si$.

with *rac*-**9a** (entry 6). Given the availability of enantioenriched epoxides,[13] this makes for a convenient entry into enantioenriched β-lactones and aldol-type products.

Epoxides **9** with additional steric hindrance in R also underwent regioselective carbonylation reactions with catalyst **7a**, and still yielded the contrasteric lactone **11** preferentially (entries 7-13). Interestingly, the selectivities observed with these

epoxides were comparable to those achieved with the less hindered epoxides **9a-e**, and even ratios as high as 32.3 and 24.0 : 1 (entries 9 and 11) were obtained. The only limitation arose when steric bulk was situated very close to the epoxide (entries 7 and 8). Nevertheless, the observed ratios of 4.9 and 1.3 : 1 in favor of lactones **11f** and **g** respectively are still good given how sterically shielded the corresponding methine-carbon is from nucleophilic attacks. This fact is also reflected in the high selectivity with which lactones **10f** and **g** are formed when using catalyst **1d** (Table 2.8, entries 6 and 7). Lastly, *cis*-epoxides with sterically very similar substituents were carbonylated with low regioselectivity by **7a**. For example, *cis*-2-butyl-3-ethyloxirane gave a ratio of 2.2 : 1 of regioisomeric β-lactones, and 30% conversion (^{1}H NMR analysis).

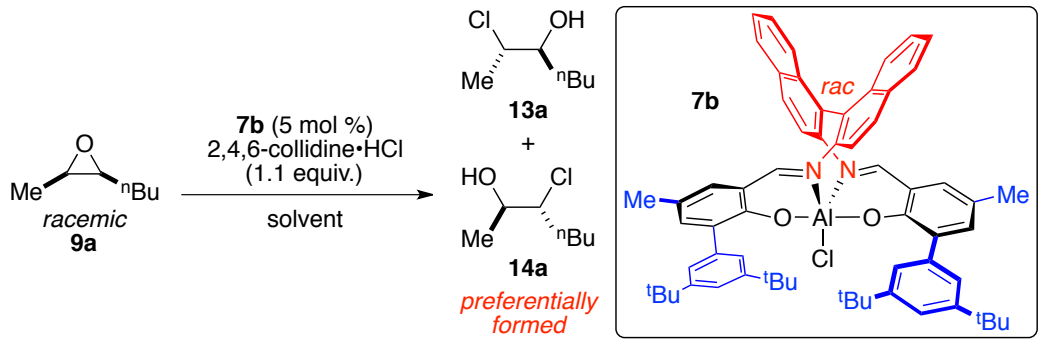
As before with catalyst **1d** (Table 2.8), the resulting *trans*-β-lactones were isolated as mixtures in good yields, except for those derived from the sterically encumbered epoxides **9f** and **g**. As was mentioned before in the discussion of the results for catalyst **1d**, conversion of the lactones into aldol-type methyl-esters using a one-pot procedure allowed for facile separation of the two regioisomers. Equally good yields were obtained using this approach, which is shown for a selected range of epoxides in Table 2.9 (entries 1-2, and 9-12).

2.3.3 Regioselective Chlorohydrin Formation Using Catalyst 7b

Lastly, use of a different nucleophile in the regioselective ring-opening of *cis*-epoxides **9** was explored. The synthesis of vicinally disubstituted chlorohydrins seemed particularly attractive because they are important functional groups,[21] yet methods for their selective synthesis are scarce.[22] Moreover, compounds of the type

[L_nAl]-Cl are commonly used as precursors in the synthesis of carbonylation catalysts, and seemed like ideal catalysts for the regioselective formation of chlorohydrins. Indeed, complex **7b** (Table 2.10), the immediate precursor to **7a**, turned out to be a selective and active catalytic system. For example, addition of 2,4,6-Me_3-pyridine (2,4,6-collidine) hydrochloride as an HCl-surrogate to *cis*-epoxide **9a** in THF in the presence of **7b** led to complete conversion of **9a** within 48 hours. Chlorohydrin **14a** was formed preferentially, and THF was the best solvent tested for this transformation (Table 2.10). The contrasteric selectivity in favor of **14a** is consistent with the carbonylation results obtained with **7a** in Table 2.9.

Table 2.10 Evaluation of solvents in the regioselective formation of chlorohydrin 14a from *cis*-disubstituted epoxide 9a using catalyst 7b[a]

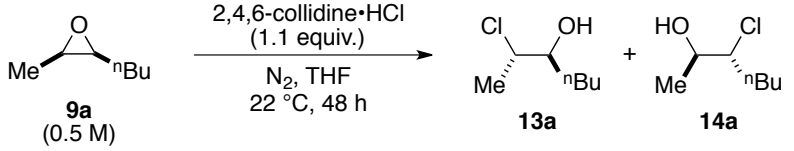
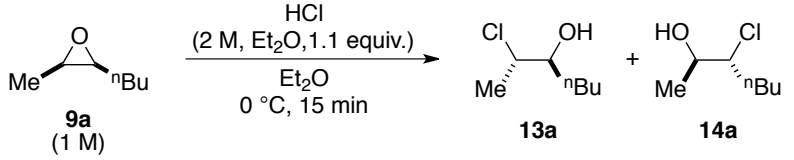
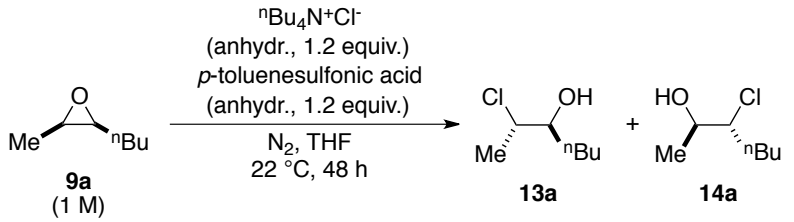
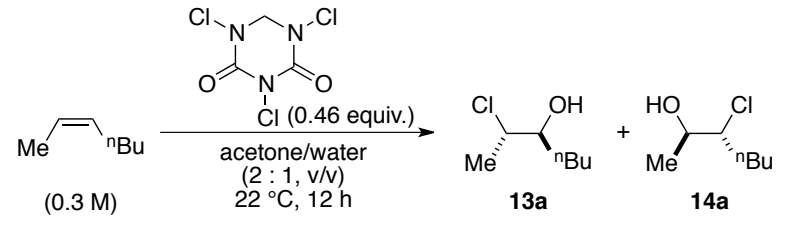


entry	solvent	ratio[b] **13a** : **14a**	conv.[b] (%)
1	THF	1 : 6.7	>95
2	1,4-dioxane	1 : 2.5	53
3	2-methyl-THF	1 : 2.3	64
4	diglyme	1 : 1.3	67
5	dimethyl carbonate	1 : 1.5	14
6	THP	1 : 4.9	78

[a]Reaction conditions: [**9a**] = 0.5 M, 22 °C, 48 h. [b]As determined by GC analysis of crude reaction mixture.

In order to ensure, that the obtained selectivities were a result of the use of **7b** and did not stem from either an inherent quality of epoxide **9a** or a background reaction involving 2,4,6-collidine hydrochloride, several control experiments were performed (Table 2.11).

Table 2.11 Control experiments concerning the regioselective formation of chlorohydrin 14a from *cis*-disubstituted epoxides

entry	reaction	ratio[a] **13a** : **14a**	conv.[a] (%)
1		1 : 1.2	<5
2		1 : 1.1	>95
3		1 : 1	>95
4		1 : 1.9	>95

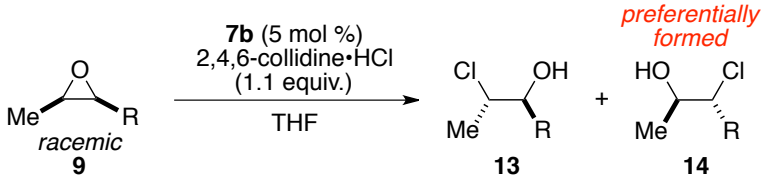
[a]As determined by ^{1}H NMR analysis of crude reaction mixture.

Entry 1 shows that the background reaction between **9a** and 2,4,6-collidine hydrochloride in the absence of **7b** is negligible, because less than 5% conversion were detected after 48 h. The low conversion can mainly be attributed to the observed low solubility of collidine hydrochloride in THF, which impedes the reaction with **9a**

in the absence of catalyst **7b**. Entries 2 and 3 examined the formation of chlorohydrins **13a** and **14a** using more soluble sources of HCl. Complete conversion of **9a** to chlorohydrin was observed in both cases, however the resulting product was a mixture of **13a** and **14a** in a ratio of almost 1 : 1. Lastly, the synthesis of chlorohydrins **13a** and **14a** starting from the olefin oxidation level was investigated using trichloroisocyanuric acid as a source of electrophilic chloronium-species. Indeed, the resulting chlorohydrins formed with excellent conversion and a slight preference in favor of **14a**, yet this outcome was still inferior to the transformation using **7b** (entry 4).

Having established the feasibility of selective chlorohydrin formation using **7b**, a number of epoxides **9** were surveyed (Table 2.12). Epoxides with linear or branched

Table 2.12 Regioselective formation of chlorohydrins 14 from *cis*-disubstituted epoxides using catalyst 7b[a]



entry	R (**epoxide**)	ratio **13** : **14**	isol. product	isol. yield (%)
1	^{n}Bu (**9a**)	1 : 6.7[b]	**14a**	68
2	^{n}Pent (**9d**)	1 : 6.1[b]	**14d**	70
3	^{n}Hex (**9e**)	1 : 6.1[c]	**14e**	77
4[d]	CH_2Ph (**9g**)	1 : 2.8[c]	**14g**	55
5	$(CH_2)_2Ph$ (**9h**)	1 : 4.9[c]	**14h**	75
6	$(CH_2)_2{}^{i}Pr$ (**9i**)	1 : 6.7[b]	**14i**	68

[a]Reaction conditions: [**9**] = 0.5 M, 22 °C, 48 h. All reactions gave full conversion (GC or ^{1}H NMR analysis). [b]As determined by GC analysis of crude reaction mixture. [c]As determined by ^{1}H NMR analysis of crude reaction mixture. [d]7.5 mol % **7b** used.

alkyl-chains as substituent R showed ratios in favor of **14** exceeding 6.0 : 1 entries (1-3, and 6). However, in cases where the steric bulk was located too close to the epoxy-group (entry 4), or became too large (entry 5), regioselectivity dropped to lower levels. Nevertheless, chlorohydrins **14** were readily isolatable in good yields.

2.3.4 Conclusion

In conclusion, two new catalysts **1d** and **7a** were introduced for the regioselective carbonylation of *racemic* and enantioenriched *cis*-disubstituted epoxides **9**. Due to the opposing regiopreference of **1d** and **7a**, either one of the two regioisomeric *trans*-β-lactones **10** and **11** could be accessed in high yield and with good selectivity. Furthermore, ring-opening of the lactone products using a one-pot procedure gave rise to *anti*-aldol-type compounds that were readily separable by column chromatography. Lastly, a structurally related catalyst **7b** was applied to the regioselective synthesis of vicinally disubstituted chlorohydrins **14** from *cis*-epoxides **9**. Similar to the carbonylation reactions with **7a**, this transformation also proceeded with synthetically useful yields and contrasteric regioselectivities.

2.4 Synopsis

Four new carbonylation catalysts were developed (Figure 2.7) and shown to be able to convert *trans*- and *cis*-disubstituted epoxides into the corresponding β-lactones with good to excellent regioselectivities and yields. Each catalyst was optimized to

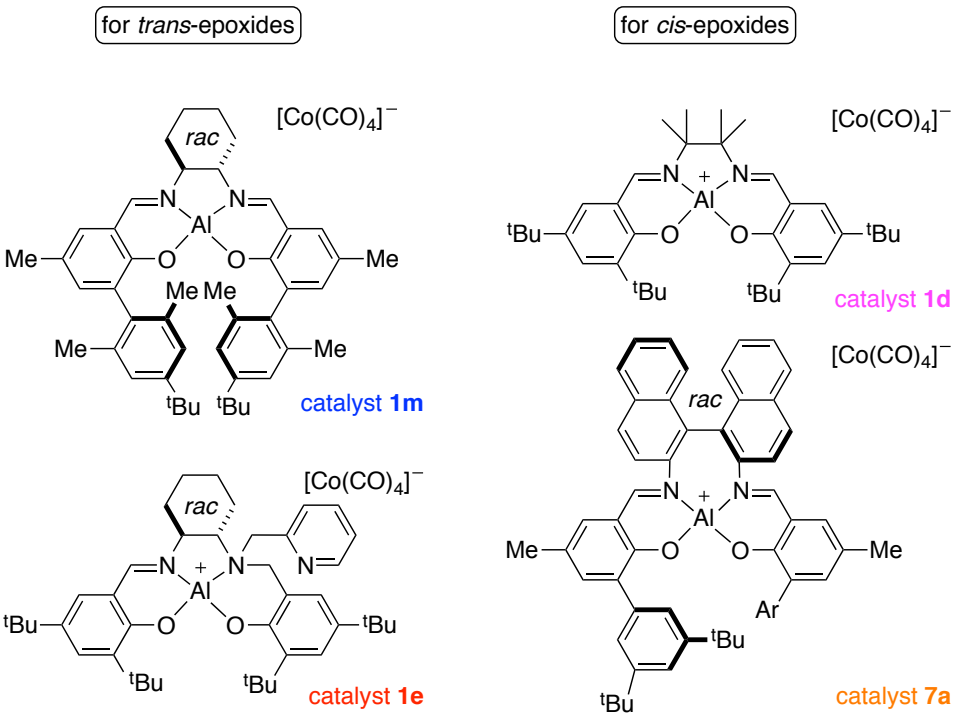


Figure 2.7 New carbonylation catalysts for the regioselective carbonylation of *cis*- and *trans*-disubstituted epoxides to β-lactones

selectively produce one different isomer out of the overall four possible isomeric β-lactones (Figure 2.8). Given these complimentary selectivities, the four catalysts provide access to an increased variety of more complex vicinally disubstituted β-lactones in a direct and synthetically useful manner starting from readily available *cis*- and *trans*-disubstituted epoxides. Overall, this study not only increases the range of available lactones, but also constitutes significant progress towards regioselective intermolecular S_N2-ring-opening reactions of *cis*- or *trans*-disubstituted epoxides, a

transformation that has eluded synthetic chemists for the longest time. Future studies will focus on enantiopure versions of these catalysts for the synthesis of enantio-enriched β-lactones *via* carbonylative kinetic resolution of *cis*- or *trans*-disubstituted epoxides.

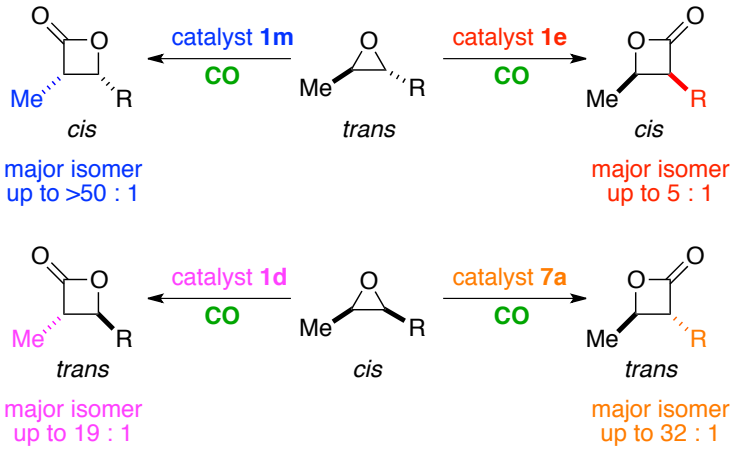


Figure 2.8 Selectivities and products achieved with each new carbonylation catalyst

2.5 Experimental Procedures

2.5.1 General Considerations

Methods and Instruments

Unless stated otherwise all synthetic manipulations were carried out using standard Schlenk techniques under a nitrogen atmosphere or in an MBraun Unilab glovebox under an atmosphere of purified nitrogen. Reactions were carried out in oven-dried glassware cooled under vacuum. High-pressure reactions were performed in a custom-designed and -fabricated, six-chamber, stainless steel, high-pressure reactor.[23] The reactor design allowed for incorporation of six 2 fluid dram glass vials.

Unless stated otherwise flash column chromatography was performed with silica gel (particle size 40-64 μm, 230-400 mesh) using either mixtures of ethyl acetate and hexanes or mixtures of diethylether and pentane as eluent. IR spectra were recorded on a Nicolet 380 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300, 400 or 500 MHz instrument at 22 °C (unless indicated otherwise) with shifts reported relative to the residual solvent peak ($CDCl_3$: 7.26 ppm (^{1}H), and 77.16 ppm (^{13}C); C_6D_6: 7.16 ppm (^{1}H) and 128.06 ppm (^{13}C)). NMR solvents were purchased from Cambridge Isotope Laboratories and stored over activated 4Å molecular sieves (C_6D_6) or K_2CO_3 ($CDCl_3$). GLC analyses were performed on a Hewlett Packard 6890 gas chromatograph equipped with a Supelco b-Dex225 column and a flame ionization detector. Helium (Airgas, UHP grade) was used as carrier gas. Elemental analyses were performed at Midwest Microlab, LLC. High-resolution mass spectrometry (HRMS) analyses were performed at the Mass Spectrometry Laboratory

at the University of Illinois at Urbana-Champaign. Optical rotations were measured on a Perkin-Elmer 241 polarimeter.

Chemicals

Anhydrous 1,4-dioxane, anhydrous dimethyl carbonate, anhydrous diethylene-glycoldimethyl ether (diglyme), and anhydrous tetrahydropyran (THP) were purchased from Sigma-Aldrich and degassed *via* three freeze-pump-thaw cycles prior to use. Anhydrous dichloromethane (DCM), toluene, hexanes and tetrahydrofuran (THF) were purchased from Fischer Scientific and sparged vigorously with nitrogen for 40 minutes prior to first use. The solvents were further purified by passing them under nitrogen pressure through two packed columns of neutral alumina (THF was also passed through a third column packed with activated 4Å molecular sieves) or through neutral alumina and copper(II) oxide (for toluene and hexanes). THF and DCM were degassed *via* three freeze-pump-thaw cycles prior to use. 2-Methyl-tetrahydrofuran, diethylether, 1,2-dimethoxyethane (DME), xylenes, anisole, and benzene were dried over sodium/benzophenone and degassed *via* three freeze-pump-thaw cycles prior to use. All other solvents were reagent grade or better and used as received. Triethylamine was dried over calcium hydride and degassed *via* three freeze-pump-thaw cycles prior to use. All epoxides used in this study were dried over calcium hydride and degassed *via* three freeze-pump-thaw cycles prior to use. Carbon monoxide (Airgas, 99.99% min. purity) was used as received. All other chemicals were purchased from Aldrich, Alfa-Aesar, Acros, TCI or GFS Chemicals, and used as received unless stated otherwise.

The following compounds were prepared according to literature procedures:

a) Catalyst-precursors: *rac*-2,4-di-*tert*-butyl-6-((*E*)-(((1*S*,2*S*)-2-((pyridin-2-yl-methyl)amino)-cyclohexyl)imino)methyl)phenol,[24] *rac*-6,6'-((1*E*,1'*E*)-((1*S*,2*S*)-cyclohexane-1,2-diylbis(azanylylidene))bis(methanylylidene))bis(2,4-dimethyl-phenol),[25] (4-(*tert*-butyl)-2,6-dimethyl-phenyl)magnesium bromide,[26] 2,3-dimethylbutane-2,3-diamine,[27] 3',5'-di-*tert*-butyl-2-hydroxy-5-methyl-[1,1'-biphenyl]-3-carbaldehyde,[28] 5-(*tert*-butyl)-2-hydroxy-3-methylbenzaldehyde,[29] 2,4,6-trimethyl-pyridine hydrochloride,[30] 4-bromo-2-(*tert*-butyl)phenol.[31]

b) Catalysts: $NaCo(CO)_4$,[32] [*rac*-salcyAl$(THF)_2$]$^+$ [$Co(CO)_4$]$^-$ (**1a**, salcy = *N*,*N*′-*bis*(3,5-di-*tert*-butyl-salicyl-idene)-1,2-cyclohexanediamine),[14a] [salphAl$(THF)_2$]$^+$ [$Co(CO)_4$]$^-$ (**1b**, salph = 6,6'-((1*E*,1'*E*)-(1,2-phenylenebis(azanylylidene))bis(meth-anylylidene))bis(2,4-di-*tert*-butylphenolate)),[12a] [salphCr$(THF)_2$]$^+$[$Co(CO)_4$]$^-$ (**1c**, salph = 6,6'-((1*E*,1'*E*)-(1,2-phenylenebis(azanylylidene))bis(methanylylidene))bis(2,4-di-*tert*-butylphenolate)),[33] [ClTPPAl$(THF)_2$]$^+$ [$Co(CO)_4$]$^-$ (**8**, ClTPP = *meso*-tetra(4-chlorophenyl)porphyrinato).[34]

c) Epoxide-precursors: (2*S*,3*R*)-2-(Benzyloxy)nonan-3-ol,[35] (*E*)-but-2-en-1-ylbenzene,[36] (*E*)-hex-4-en-1-ol,[37] (*E*)-pent-3-en-1-ol,[38] (*S*)-2-(benzyloxy)-1-(pyrrolidin-1-yl)propan-1-one,[39] (*Z*)-*tert*-butyldimethyl(pent-3-en-1-yloxy)silane,[40] (*Z*)-but-2-en-1-ylbenzene,[41] (*Z*)-1-phenyl-3-pentene.[42]

d) Epoxides: *rac*-(2*S*,3*S*)-2-ethyl-3-methyloxirane (**2b**),[43] *rac*-(2*S*,3*S*)-2-butyl-3-methyloxirane (**2d**),[44] *rac*-(2*S*,3*S*)-2-butyl-3-ethyloxirane (**2k**),[45] *rac*-(2*S*,3*S*)-2-methyl-3-pentyloxirane (**2a**),[44] *rac*-(2*S*,3*S*)-2-hexyl-3-methyl-oxirane (**2e**),[44] *rac*-*tert*-butyldimethyl(((2*S*,3*S*)-3-methyloxiran-2-yl)methoxy)-silane (**2h**),[46] *rac*-(2*S*,3*S*)-2-

isopropyl-3-methyloxirane (**2j**),[47] *rac*-(2*S*,3*R*)-2-ethyl-3-methyloxirane (**9b**),[48] *rac*-(2*R*,3*S*)-2-methyl-3-propyloxirane (**9c**),[48] *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane (**9a**),[49] (2*R*,3*S*)-2-butyl-3-methyloxirane ((2*R*,3*S*)-**9a**),[48] *rac*-(2*R*,3*S*)-2-butyl-3-ethyloxirane,[50] *rac*-(2*R*,3*S*)-2-methyl-3-pentyloxirane (**9d**),[48] *rac*-(2*S*,3*R*)-2-hexyl-3-methyloxirane (**9e**),[48] *rac*-(2*S*,3*R*)-2-isopentyl-3-methyloxirane (**9i**),[48] *rac-tert*-butyldimethyl(3-((2*S*,3*R*)-3-methyloxiran-2-yl)propoxy)silane (**9k**),[48] *rac-cis*-1-acetoxy-4,5-epoxyhexane (**9l**).[51]

2.5.2 Synthetic Procedures

2.5.2.1 General Procedures

General procedure A: Epoxidation of alkenes to epoxides using *m*CPBA

*m*CPBA (Aldrich, ≤ 77%) was added in portions at 0 °C under air to a solution of the corresponding alkene in DCM, and the resulting mixture was stirred at the same temperature until TLC analysis indicated complete consumption of the alkene. After destroying excess *m*CPBA by adding aqueous $NaHSO_3$ at 0 °C, the reaction mixture was filtered, the organic phase washed with $NaHCO_3$ (aq., sat., 3x), then dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified either *via* distillation or flash column chromatography.

General procedure B: Kumada coupling of aryl-Grignard reagents with 2-bromo-phenols

The appropriate bromophenol (distilled or sublimed prior to use) was added in small portions to a mixture of sodium hydride (Aldrich, dry, 95%) and THF at 0 °C,

followed by stirring at 22 °C for 10 minutes. $Pd(acac)_2$ (Strem) or $Pd(OAc)_2$ (Strem) was added, followed by the appropriate Grignard reagent, and the resulting mixture was refluxed for 12 h. Upon cooling to 0 °C, H_2O was carefully added to destroy residual Grignard reagent and sodium hydride. HCl (aq., 2 M) was added followed by celite, and the resulting mixture was filtered through a pad of celite. The resulting phases were separated and the aqueous phase extracted with Et_2O (3x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified *via* flash column chromatography.

General procedure C: Formylation of 2-arylphenols to the corresponding salicylaldehyde derivatives

Methylmagnesium bromide (Acros, Et_2O, 3 M) was added slowly to the appropriate 2-arylphenol in THF at 0 °C. After warming to 22 °C, toluene, triethylamine and paraformaldehyde were added, and the resulting reaction mixture stirred at 80 °C for 12 h. After cooling to 0 °C, H_2O and then HCl (aq., 2 M) were added, and the resulting phases were separated. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography.

General procedure D: Assembly of salen-compounds *via* imine-condensation

The appropriate salicylaldehyde derivative was mixed under air with either methanol or ethanol at the indicated temperature. The appropriate diamine was added and the reaction mixture stirred at the same temperature for the time indicated. The reaction mixture was allowed to reach 22 °C, and the resulting precipitate was isolated by filtration, followed by washings with small amounts of cold methanol or ethanol to give the corresponding salen-compound after drying *in vacuo* at 80 °C.

General procedure E: Metallation of salen-compounds using Et_2AlCl

The appropriate salen-compound was dissolved in the indicated amount of DCM and cooled to 0 °C. Et_2AlCl (Aldrich, 1.0 M, hexanes, *pyrophoric*) is added in one portion under vigorous stirring at 0 °C, and the resulting solution was stirred at 22 °C for 12 h. The resulting metal-complex was then isolated as indicated.

General procedure F: Regioselective carbonylation of *trans*-epoxides 2 using catalyst 1e

In a glove box, a 2 fluid dram glass vial equipped with a Teflon-coated magnetic stir bar was charged with the appropriate amount of catalyst **1e** and benzene. The vial was then placed in a custom-made 6-well high-pressure reactor which itself was placed in a glove box freezer at -34 °C for 30 minutes. The appropriate amount of epoxide (also cooled to -34 °C) was then added to the vial, the reactor removed from the freezer, subsequently sealed, taken out of the glove box, placed in a well-ventilated hood and pressurized with carbon monoxide (900 psi). It is important to keep the

temperature of the reactor below 0 °C once it is removed from the freezer to minimize isomerization of the epoxide to ketone products. The reactor was then placed in a 22 °C water bath, and the reaction mixture stirred for 22 h. The reactor was carefully vented in a well-ventilated hood, the crude reaction mixture concentrated under reduced pressure and then purified further *via* flash column chromatography unless indicated otherwise.

General procedure G: Regioselective carbonylation of *trans*-epoxides 2 using catalyst 1m prepared *in situ*

In a glove box, a 2 fluid dram glass vial equipped with a Teflon-coated magnetic stir bar was charged with **MF9** (the precursor to **1m**) and a stocksolution of $NaCo(CO)_4$ in THF. After 1 minute of stirring at 22 °C, the vial was placed in a custom-made 6-well high-pressure reactor which itself was placed in a glove box freezer (-34 °C) for 30 minutes. The appropriate amount of epoxide (also cooled to -34 °C) was then added to the vial, the reactor removed from the freezer, subsequently sealed, taken out of the glove box, placed in a well-ventilated hood and pressurized with carbon monoxide (900 psi) It is important to keep the temperature of the reactor below 0 °C once it is removed from the freezer to minimize isomerization of the epoxide to ketone products. The reactor was then placed in a 22 °C water bath, and the reaction mixture stirred for 20 h. The reactor was carefully vented in a well-ventilated hood and the product purified as indicated.

Note: No significant difference was observed when conducting regioselective carbonylations of *trans*-epoxides **2** using isolated batches of catalyst **1m** instead of *in*

situ prepared **1m**. Overall, *in situ* formation was found to be more convenient because the precursor **MF9** is significantly less sensitive to oxygen and can be stored at 22 °C.

General procedure H: Regioselective carbonylation of *cis*-epoxides using catalyst 1d

In a glove box, a 2 fluid dram glass vial equipped with a Teflon-coated magnetic stir bar was charged with catalyst **1d** and THF. The vial was then placed in a custom-made 6-well high-pressure reactor which itself was placed in a glove box freezer at -34 °C for 30 minutes. The appropriate epoxide (also cooled to -34 °C) was then added to the vial, the reactor removed from the freezer, subsequently sealed, taken out of the glove box, placed in a well-ventilated hood and pressurized with carbon monoxide (900 psi). It is important to keep the temperature of the reactor below 0 °C once it is removed from the freezer to minimize isomerization of the epoxide to ketone products. The reactor was then sealed again, placed in a 22 °C water bath, and stirred for the time indicated. The reactor was carefully vented in a well-ventilated hood, the crude reaction mixture concentrated under reduced pressure and the product isolated as indicated.

General procedure I: Regioselective carbonylation of epoxides with *in situ* formation of catalyst 7a

In a glove box, a 2 fluid dram glass vial equipped with a Teflon-coated magnetic stir bar was charged with **7b** (the precursor to **7a**), $NaCo(CO)_4$, and dioxane. The vial was then placed in a custom-made 6-well high-pressure reactor, which itself was

placed in a glove box freezer at -34 °C for 30 minutes. The appropriate epoxide (also cooled to -34 °C) was added to the vial, the reactor removed from the freezer, subsequently sealed, taken out of the glove box, placed in a well-ventilated hood and pressurized with carbon monoxide (900 psi). It is important to keep the temperature of the reactor below 0 °C once it is removed from the freezer to minimize isomerization of the epoxide to ketone products. The reactor was then sealed again, placed in a 22 °C water bath and stirred for the time indicated. The product was then isolated as indicated.

General procedure J: Regioselective chlorohydrin formation using catalyst 7b

In a glove box, a 2 fluid dram glass vial equipped with a Teflon-coated magnetic stir bar was charged with catalyst **7b**, 2,4,6-trimethylpyridine hydrochloride, THF, and the appropriate epoxide. The vial was sealed with a Teflon-coated cap, and the reaction mixture stirred at 22 °C for 48 h. The crude reaction mixture was concentrated under reduced pressure and the product isolated as indicated.

2.5.2.2 Synthesis of Starting Materials

***rac*-(2*S*,3*S*)-2-Methyl-3-propyloxirane (2c)**

Following general procedure A, (*E*)-hex-2-ene (4.70 g, 55.8 mmol) was reacted with *m*CPBA (17.0 g) in DCM (135 ml) to give **2c** (1.77 g, 32%) as a colorless liquid. The analytical data was in accordance with that reported in the literature.[52] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.72 (qd, *J* = 5.3, 2.3 Hz, 1H), 2.61 (dt, *J* = 5.6, 2.5 Hz, 1H),

1.51–1.39 (m, 4H), 1.28 (d, J = 5.2 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 59.8, 54.7, 34.2, 19.4, 17.8, 14.0.

(2*S*,3*S*)-2-Hexyl-3-methyloxirane ((2*S*,3*S*)-2e)

(2*S*,3*R*)-2-(Benzyloxy)nonan-3-ol[35] (3.59 g, 14.3 mmol) was dissolved in pyridine (18 ml), and *para*-toluenesulfonylchloride (7.69 g, 40.3 mmol) was added. After stirring at 40 °C for 24 hours, ethylene glycol (7.5 ml) was added at 22 °C, followed by stirring at 22 °C for one hour to destroy excess *para*-toluenesulfonylchloride. The reaction mixture was then diluted with Et_2O, washed with hydrochloric acid (aq., 1 M, 3x), dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude product was filtered through silica gel using a 10:1-mixture of hexanes and Et_2O, and the filtrate concentrated under reduced pressure. The residue was taken up in methanol (100 ml), palladium on carbon (Strem, 5% Pd, 1.33 g) was added, and the resulting suspension stirred vigorously at 22 °C under an atmosphere of hydrogen (1 atm) for five hours. The reaction mixture was diluted with Et_2O, filtered through a pad of celite, and then concentrated. The residue was taken up in methanol (25 ml), potassium carbonate (11.4 g, 82.5 mmol) was added, and the resulting mixture stirred at 22 °C for 90 minutes. The supernatant was decanted, and the remaining solid washed repeatedly with DCM. The combined organic phases were washed with water, then brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to give (2*S*,3*S*)-**2e** (1.41 g, 71% over three steps) as a colorless liquid. The NMR-spectroscopic data was in accordance with that reported in the literature for the *racemic* compound.[44] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 2.71 (qd, J = 5.2, 2.3 Hz, 1H), 2.60 (td, J = 5.6, 2.2 Hz,

1H), 1.52–1.26 (m, 10H), 1.27 (d, J = 5.2 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 60.0, 54.7, 32.2, 31.9, 29.2, 26.1, 22.7, 17.8, 14.2. **Specific rotation**: $[\alpha]^{22}_D$ = -48 (c = 3.3, pentanes).

Using an NMR shift-reagent,[53] the enantiomeric ratio (er) of (2*S*,3*S*)-**2e** was determined to be 2.3 : 97.7 by ^{1}H NMR analysis in comparison to authentic *racemic* material. NMR samples were prepared by mixing 26 mg of the respective epoxide with 7.7 mg of europium(III) tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate] as shift-reagent in 0.6 ml C_6D_6.

***rac*-*Tert*-butyldimethyl(3-((2*S*,3*S*)-3-methyloxiran-2-yl)propoxy)silane (2f)**

To a solution of (*E*)-hex-4-en-1-ol[37] (2.57 g, 8.32 mmol), DCM (20 ml) and 1-methyl-1*H*-imidazole (2.03 g, 24.7 mmol) was added a solution of *tert*-butylchlorodimethylsilane (1.74 g, 11.5 mmol) in DCM (6 ml) at 22 °C. The reaction mixture was stirred for 19 h, then washed with water, dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude product was filtered through silica gel using a 95:5-mixture of hexanes and ethylacetate, and the filtrate concentrated under reduced pressure. The residue was then taken up in DCM (20 ml), *m*CPBA (Aldrich, ≤ 77%, 2.50 g) was added in portions at 0 °C, and the resulting mixture stirred at the same temperature for 4 h. After destroying excess *m*CPBA by adding aqueous $NaHSO_3$ at 0 °C, DCM was added, and the organic phase washed with $NaHCO_3$ (aq., sat., 3x), then dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to give **2f** (6.35 g, 76%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.67–3.58 (m,

2H), 2.74 (qd, *J* = 5.2, 2.3 Hz, 1H), 2.64 (ddd, *J* = 6.2, 4.8, 2.3 Hz, 1H), 1.71–1.48 (m, 4H), 1.28 (d, *J* = 5.2 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 62.8, 59.7, 54.8, 29.3, 28.7, 26.1, 18.5, 17.8, -5.2. **IR** (neat, cm^{-1}): 2929, 2857, 1472, 1254, 1093, 833, 773. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{27}O_2Si^+$ ($M + H^+$) 231.1775, found 231.1790.

***rac*-*Tert*-butyldimethyl(2-((2*S*,3*S*)-3-methyloxiran-2-yl)ethoxy)silane (2h)**

To a solution of (*E*)-pent-3-en-1-ol[38] (1.94 g, 6.58 mmol), DCM (16 ml) and 1-methyl-1*H*-imidazole (1.61 g, 19.6 mmol) was added a solution of *tert*-butylchlorodimethylsilane (1.38 g, 9.09 mmol) in DCM (5 ml) at 22 °C. The reaction mixture was stirred for 19 h, then washed with water, dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude product was filtered through silica gel using a 95:5-mixture of hexanes and ethylacetate, and the filtrates concentrated under reduced pressure. The residue was then taken up in DCM (16 ml), *m*CPBA (Aldrich, ≤ 77%, 2.00 g) was added in portions at 0 °C, and the resulting mixture stirred at the same temperature for 4 h. After destroying excess *m*CPBA by adding aqueous $NaHSO_3$ at 0 °C, DCM was added, and the organic phase washed with $NaHCO_3$ (aq., sat., 3x), then dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to give **2h** (0.790 g, 55%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.74 (dd, *J* = 6.9, 5.4 Hz, 2H), 2.80–2.73 (m, 2H), 1.79–1.64 (m, 2H), 1.30 (d, *J* = 5.2 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 60.1, 57.5, 54.9, 35.6, 26.0, 18.4,

17.8, -5.3. **IR** (neat, cm^{-1}): 2928, 2857, 1472, 1252, 1097, 832, 773. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{25}O_2Si^+$ ($M + H^+$) 217.1618, found 217.1625.

***rac*-(2*S*,3*S*)-2-Benzyl-3-methyloxirane (2i)**

Following general procedure A, (*E*)-but-2-en-1-ylbenzene[36] (2.15 g, 16.3 mmol) was reacted with *m*CPBA (4.90 g) in DCM (40 ml) to give **2i** (1.73 g, 78%) as a colorless liquid. The analytical data was in accordance with that reported in the literature.[20] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34–7.29 (m, 2H), 7.26–7.22 (m, 3H), 2.94–2.78 (m, 4H), 1.31 (d, *J* = 5.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 137.6, 129.1, 128.7, 126.7, 59.8, 54.7, 38.6, 17.7.

(2*R*,3*S*)-3-(Benzyloxy)-1-phenylbutan-2-ol (SM1)

Adapting a published procedure,[54] (*S*)-2-(benzyloxy)-1-(pyrrolidin-1-yl)propan-1-one[39] (4.63 g, 19.8 mmol) was dissolved in THF (20 ml) and cooled to -20 °C. Benzylmagnesium chloride (Aldrich, Et_2O, 1.0 M, 40 ml, 40.0 mmol) was added dropwise at -20 °C, the resulting mixture stirred at the same temperature for 30 minutes, followed by addition of ammonium chloride (aq., sat.). The reaction mixture was then extracted with Et_2O (3x). The combined organic phases were dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography to give (*S*)-3-(benzyloxy)-1-phenylbutan-2-one (ca. 3.74 g, ca. 74%) as a colorless liquid. *Note*: The isolated material contained ca. 0.900 g of (*S*)-2-benzyl-3-(benzyloxy)-1-phenylbutan-2-ol as an inseparable impurity, and was used in the next step without further purification. NMR-spectroscopic data for the main component is provided: **^{1}H NMR** (500 MHz, $CDCl_3$):

δ 7.39–7.20 (m, 10H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.04 (q, *J* = 6.9 Hz, 1H), 3.89 (d, *J* = 15.8 Hz, 1H), 3.88 (d, *J* = 15.8 Hz, 1H), 1.39 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 209.9, 137.6, 133.9, 129.8, 128.7, 128.6, 128.0, 128.0, 127.0, 80.2, 72.0, 44.6, 17.5.

The impure (*S*)-3-(benzyloxy)-1-phenylbutan-2-one (ca. 3.74 g, ca. 14.7 mmol) was added to a suspension of lithium bis((trifluoromethyl)sulfonyl)amide (4.47 g, 17.9 mmol) in DCM (45 ml) and cooled to -78 °C. Sodium triethylborohydride (Aldrich, toluene, 1.0 M, 29 ml, 29.0 mmol) was added dropwise at -78 °C, and the resulting reaction mixture stirred at -78 °C for one hour. Ammonium chloride (aq., sat.) was added, followed by hydrochloric acid (aq., 1 M), and the resulting mixture was then extracted with DCM (3x). The combined organic phases were dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **SM1** (1.32 g, 26% over two steps) as a colorless liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.35–7.20 (m, 10H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.02–3.95 (m, 1H), 3.58–3.50 (m, 1H), 2.86–2.70 (m, 2H), 2.01 (d, *J* = 3.6 Hz, 1H), 1.27 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 138.7, 138.6, 129.4, 128.6, 128.5, 127.78, 127.76, 126.5, 77.3, 74.5, 70.9, 39.0, 14.1. **IR** (neat, cm^{-1}): 3455, 3027, 2686, 14958, 1453, 1070, 1028. **HRMS** (ESI) *m/z* calculated for $C_{17}H_{21}O_2^+$ ($M + H^+$) 257.1536, found 257.1541. **Specific rotation**: $[\alpha]^{22}_D$ = +39.5 (*c* = 0.35, $CHCl_3$).

(2*S*,3*S*)-2-Benzyl-3-methyloxirane ((2*S*,3*S*)-2i)

(2*R*,3*S*)-3-(Benzyloxy)-1-phenylbutan-2-ol (**SM1**, 1.32 g, 5.15 mmol) was dissolved in pyridine (6.5 ml), and *para*-toluenesulfonylchloride (3.44 g, 18.0 mmol) was added. After stirring at 40 °C for 24 hours, ethylene glycol (2.7 ml) was added at 22 °C, followed by stirring at 22 °C for one hour to destroy excess *para*-toluenesulfonylchloride. The reaction mixture was then diluted with Et_2O, washed with hydrochloric acid (aq., 1 M, 3x), dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude product was filtered through silica gel using a 6:1-mixture of hexanes and Et_2O, and the filtrate concentrated under reduced pressure. The residue was then taken up in a mixture of methanol (35 ml) and ethylacetate (15 ml), palladium on carbon (Strem, 5% Pd, 1.33 g) was added, and the resulting suspension stirred vigorously at 22 °C under an atmosphere of hydrogen (1 atm) for five hours. The reaction mixture was diluted with Et_2O, filtered through a pad of celite, and then concentrated. The residue was then taken up in methanol (8 ml), potassium carbonate (3.86 g, 27.9 mmol) was added, and the resulting mixture stirred at 22 °C for 90 minutes. The supernatant was decanted, and the remaining solid washed repeatedly with DCM. The combined organic phases were washed with water, then brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to give (2*S*,3*S*)-**2i** (0.495 g, 65% over three steps) as a colorless liquid. The analytical data was in accordance with that reported in the literature.[55] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.33–7.30 (m, 2H), 7.26–7.23 (m, 3H), 2.94–2.79 (m, 4H), 1.31 (d, *J* = 5.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 137.6, 129.1, 128.7, 126.7, 59.8, 54.7, 38.6, 17.7.

Specific rotation: $[\alpha]^{22}_{D}$ = -21 (*c* = 0.61, $CHCl_3$). The enantiomeric ratio (er) was determined to be >99.5 : 0.5 by GLC analysis (b-Dex225 column) in comparison to authentic *racemic* material.

***rac*-(2*S*,3*R*)-2-(Cyclohexylmethyl)-3-methyloxirane (9f)**

Methyllithium (Acros, 1.6 M, Et_2O, 21.5 ml, 34.4 mmol) was added dropwise at -78 °C to a solution of prop-2-yn-1-ylcyclohexane (3.81 g, 31.2, mmol) in THF (55 ml), and the resulting solution stirred at -78 °C for 0.5 h. Methyl iodide (10.5 g, 74.0 mmol) was added dropwise at -78 °C, the reaction mixture slowly warmed to 22 °C and stirred for 12 h. $NaHCO_3$ (sat., aq.) was added and the aqueous phase extracted with pentane. The combined organic layers were dried with sodium sulfate, filtered and concentrated under reduced pressure. THF (14 ml) was added to the residue and the resulting solution degassed by two freeze-pump-thaw cycles. The solution was then added to a solution of 9-BBN (0.5 M, THF, 72 ml) at 0 °C, and the resulting reaction mixture stirred at 22 °C until TLC analysis indicated complete disappearance of the alkyne. Methanol (1.0 ml) was added, then glacial acetic acid (20.0 mg) as a solution in methanol (2.6 ml), and the resulting mixture stirred for 2 h at 22 °C. Pentane was added, followed by controlled addition of NaOH (1 M, aq., 40 ml) and H_2O_2 (30%, aq., 20 ml) under ice cooling. The aqueous layer was extracted with pentane, and the combined organic layers washed with $NaHCO_3$ (aq., sat.), then dried with sodium sulfate, filtered and concentrated under reduced pressure. The crude product was filtered through a plug of silica gel using pentane, and the filtrates concentrated under reduced pressure.

Following general procedure A, the residue was reacted with *m*CPBA (9.00 g) in DCM (40 ml) to give **9f** (1.12 g, 23%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.02 (dtd, *J* = 5.3, 4.3 Hz, 1H), 2.94 (td, *J* = 6.0, 4.2 Hz, 1H), 1.79–1.62 (m, 5H), 1.51–1.33 (m, 3H), 1.30–1.08 (m, 3H), 1.25 (d, *J* = 5.5 Hz, 3H), 1.04–0.89 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 56.0, 52.7, 36.2, 35.0, 33.8, 33.3, 26.6, 26.41, 26.38, 13.5. **IR** (neat, cm^{-1}): 2921, 2851, 1448, 1390, 961, 889, 819, 783. **HRMS** (ESI) *m/z* calculated for $C_{10}H_{19}O^+$ ($M + H^+$) 155.1430, found 155.1443.

***rac*-(2*S*,3*R*)-2-Benzyl-3-methyloxirane (9g)**

Following general procedure A, (*Z*)-but-2-en-1-ylbenzene[41] (0.446 g, 3.37 mmol) was reacted with *m*CPBA (0.960 g) in DCM (17 ml) to give **9g** (0.390 g, 78%) as a colorless liquid. The analytical data was in accordance with that reported in the literature.[56] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35–7.31 (m, 2H), 7.27–7.23 (m, 3H), 3.18–3.11 (m, 2H), 2.94 (dd, *J* = 14.7, 5.8 Hz, 1H), 2.79 (dd, *J* = 14.7, 6.3 Hz, 1H), 1.41 (d, *J* = 5.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 137.9, 128.9, 128.7, 126.6, 57.4, 53.0, 34.2, 13.6.

***rac*-(2*R*,3*S*)-2-Methyl-3-phenethyloxirane (9h)**

Following general procedure A, (*Z*)-1-phenyl-3-pentene[42] (2.71 g, 18.5 mmol) was reacted with *m*CPBA (5.50 g) in DCM (45 ml) to give **9h** (2.19 g, 73%) as a colorless liquid. The analytical data was in accordance with that reported in the literature.[42] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31–7.28 (m, 2H), 7.22–7.18 (m, 3H), 3.04 (qd, *J* = 5.5, 4.2 Hz, 1H), 2.95 (td, *J* = 6.3, 4.3 Hz, 1H), 2.85 (ddd, *J* = 14.6, 9.2,

5.8 Hz, 1H), 2.74 (ddd, *J* = 13.9, 8.9, 7.4 Hz, 1H), 1.93–1.69 (m, 2H), 1.19 (d, *J* = 5.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 141.5, 128.55, 128.55, 126.2, 56.6, 53.0, 32.8, 29.6, 13.3.

***rac*-*Tert*-butyldimethyl(2-((2*S*,3*R*)-3-methyloxiran-2-yl)ethoxy)silane (9j)**

Following general procedure A, (*Z*)-*tert*-butyldimethyl(pent-3-en-1-yloxy)silane[40] (2.74 g, 13.7 mmol) was reacted with *m*CPBA (4.10 g) in DCM (35 ml) to give **9j** (2.34 g, 79%) as a colorless liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.80–3.75 (m, 2H), 3.09–3.03 (m, 2H), 1.82–1.63 (m, 2H), 1.26 (d, *J* = 5.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 60.6, 54.8, 52.7, 31.2, 26.1, 18.5, 13.6, -5.2. **IR** (neat, cm^{-1}): 2929, 2857, 1472, 1254, 1094, 829, 774. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{24}NaO_2Si^+$ ($M + Na^+$) 239.1438, found 239.1445.

2',5,6'-Trimethyl-[1,1'-biphenyl]-2-ol (SM2)

Following general procedure B, 2-bromo-4-methylphenol (3.77 g, 20.2 mmol) was treated with sodium hydride (0.70 g, 29.2 mmol) in THF (40 ml), followed by addition of $Pd(acac)_2$ (0.302 g, 0.991 mmol, 4.90 mol %), and 2,6-xylylmagnesium bromide (Aldrich, THF, 1.0 M, 30 ml, 30 mmol) to give **SM2** (3.16 g, 74%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36–7.24 (m, 3H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.92 (s, 1H), 4.55 (s, 1H), 2.40 (s, 3H), 2.15 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 150.1, 138.0, 135.1, 130.2, 130.0, 129.6, 128.4, 128.0, 126.3, 115.1, 20.7, 20.5. **IR** (neat, cm^{-1}): 3493, 2919, 1496, 1461, 1274, 1187, 1036,

816, 771. **HRMS** (ESI) *m/z* calculated for $C_{15}H_{17}O^+$ (M + H^+) 212.1201, found 212.1207.

2-Hydroxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-carbaldehyde (SM3)

Following general procedure C, 2',5,6'-trimethyl-[1,1'-biphenyl]-2-ol (**SM2**, 3.14 g, 14.8 mmol) was treated with methylmagnesium bromide (6.0 ml, 18.0 mmol) in THF (40 ml), followed by addition of toluene (75 ml), triethylamine (3.6 ml, 25.8 mmol), and paraformaldehyde (1.26 g, 42.0 mmol) to give **SM3** (2.91 g, 87%) as a colorless solid. **MP** 64–65 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.96 (s, 1H), 9.93 (s, 1H), 7.39–7.38 (m, 1H), 7.21 (dd, *J* = 8.3, 6.7 Hz, 1H), 7.18 (d, *J* = 2.3 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 2H), 2.39 (s, 3H), 2.06 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 196.8, 156.7, 139.3, 136.7, 135.9, 132.9, 129.7, 129.2, 127.9, 127.4, 120.7, 20.6, 20.5. **IR** (neat, cm^{-1}): 2919, 2850, 1643, 1439, 1315, 1261, 1220, 1123, 975, 869, 774. **HRMS** (ESI) *m/z* calculated for $C_{16}H_{17}O_2^+$ (M + H^+) 241.1223, found 241.1228.

2',4',6'-Trimethyl-[1,1'-biphenyl]-2-ol (SM4)

Following general procedure B, 2-bromophenol (3.13 g, 18.1 mmol) was treated with sodium hydride (0.61 g, 25.4 mmol) in THF (35 ml), followed by addition of $Pd(acac)_2$ (0.258 g, 0.847 mmol, 4.68 mol %), and mesitylmagnesium bromide (Aldrich, THF, 1.0 M, 28 ml, 28.0 mmol) to give **SM4** (3.77 g, 98%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29 (ddd, *J* = 8.8, 6.8, 2.1 Hz, 1H), 7.04–6.97 (m, 5H), 4.64 (s, 1H), 2.36 (s, 3H), 2.04 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 152.6, 138.2, 137.9, 131.7, 130.2, 129.0, 128.9, 126.5, 120.8, 115.2, 21.2, 20.3. **IR** (neat, cm^{-}

^{1}): 3491, 2918, 1580, 1474, 1334, 1227, 1185, 1005, 851, 753. **HRMS** (EI) *m/z* calculated for $C_{15}H_{16}O^{+}$ (M^{+}) 212.1201, found 212.1205.

2-Hydroxy-2',4',6'-trimethyl-[1,1'-biphenyl]-3-carbaldehyde (SM5)

Following general procedure C, 2',4',6'-trimethyl-[1,1'-biphenyl]-2-ol (**SM4**, 3.74 g, 17.6 mmol) was treated with methylmagnesium bromide (7.0 ml, 21.0 mmol) in THF (45 ml), followed by addition of toluene (84 ml), triethylamine (4.0 ml, 28.7 mmol), and paraformaldehyde (1.34 g, 44.6 mmol) to give **SM5** (3.76 g, 89%) as a colorless solid. **MP** 95–97 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.15 (s, 1H), 9.98 (s, 1H), 7.61 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.36 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.99 (s, 2H), 2.36 (s, 3H), 2.04 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 196.8, 158.9, 138.6, 137.6, 136.6, 133.1, 132.8, 130.0, 128.3, 120.9, 120.0, 21.3, 20.4. **IR** (neat, cm^{-1}): 2917, 2883, 1656, 1614, 1433, 1392, 1295, 1218, 1057, 907, 823, 743. **HRMS** (ESI) *m/z* calculated for $C_{16}H_{17}O_2^{+}$ ($M + H^{+}$) 241.1223, found 241.1232.

2',4',5,6'-Tetramethyl-[1,1'-biphenyl]-2-ol (SM6)

Following general procedure B, 2-bromo-4-methylphenol (2.33 g, 12.4 mmol) was treated with sodium hydride (0.380 g, 15.8 mmol) in THF (20 ml), followed by addition of $Pd(acac)_2$ (0.170 g, 0.558 mmol, 4.50 mol %), and mesitylmagnesium bromide (Aldrich, THF, 1.0 M, 18 ml, 18.0 mmol) to give **SM6** (2.78 g, 99%) as an off-white solid. **MP** 66–67 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 2H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.82 (s, 1H), 4.49 (d, *J* = 0.9 Hz, 1H), 2.35 (s, 3H), 2.32 (s, 3H), 2.04 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.3, 138.0, 137.8,

132.0, 130.5, 129.9, 129.5, 128.8, 126.3, 114.9, 21.2, 20.7, 20.4. **IR** (neat, cm^{-1}): 3477, 2917, 1478, 1436, 1272, 1230, 1161, 1031, 819. **HRMS** (ESI) *m/z* calculated for $C_{16}H_{18}NaO^+$ ($M + Na^+$) 249.1250, found 249.1259.

2-Hydroxy-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-carbaldehyde (SM7)

Following general procedure C, 2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol (**SM6**, 3.78 g, 16.7 mmol) was treated with methylmagnesium bromide (6.5 ml, 19.5 mmol) in THF (40 ml), followed by addition of toluene (80 ml), triethylamine (2.76 g, 27.3 mmol), and paraformaldehyde (1.28 g, 42.6 mmol) to give **SM7** (3.32 g, 78%) as an off-white solid. **MP** 105–106 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.95 (s, 1H), 9.93 (s, 1H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.18 (d, *J* = 2.2 Hz, 1H), 6.97 (s, 2H), 2.39 (s, 3H), 2.34 (s, 3H), 2.03 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.8, 156.9, 139.5, 137.4, 136.6, 132.9, 132.8, 129.8, 129.2, 128.3, 120.6, 21.3, 20.45, 20.42. **IR** (neat, cm^{-1}): 2917, 1643, 1454, 1320, 1224, 1103, 971, 850, 798, 742. **HRMS** (ESI) *m/z* calculated for $C_{17}H_{19}O^+$ ($M + H^+$) 255.1380, found 255.1383.

4'-(*Tert*-butyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-2-ol (SM8)

Following general procedure B, 2-bromo-4-methylphenol (3.88 g, 20.7 mmol) was treated with sodium hydride (0.680 g, 28.3 mmol) in THF (40 ml), followed by addition of $Pd(OAc)_2$ (0.220 g, 0.980 mmol, 4.73 mol %), and (4-(*tert*-butyl)-2,6-dimethyl-phenyl)magnesium bromide[26] (THF, 1.0 M, 40 ml) to give **SM8** (4.58 g, 83%) as a thick yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.18 (s, 2H), 7.08 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 4.51 (s, 1H), 2.31 (s, 3H), 2.08 (s, 6H), 1.37 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 151.2, 150.4, 137.5,

131.9, 130.4, 129.8, 129.5, 126.4, 125.1, 114.9, 34.6, 31.5, 20.8, 20.7. **IR** (neat, cm^{-1}): 3543, 2962, 1606, 1481, 1362, 1227, 1186, 1035, 869, 815. **HRMS** (ESI) *m/z* calculated for $C_{19}H_{24}NaO^+$ ($M + Na^+$) 291.1719, found 291.1730.

4'-(*Tert*-butyl)-2-hydroxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-carbaldehyde (SM9)

Following general procedure C, 4'-(*tert*-butyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-2-ol (**SM8**, 4.40 g, 16.4 mmol) was treated with methylmagnesium bromide (6.5 ml, 19.5 mmol) in THF (40 ml), followed by addition of toluene (80 ml), triethylamine (2.90 g, 28.7 mmol), and paraformaldehyde (1.33 g, 44.3 mmol) to give **SM9** (4.36 g, 90%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.99 (s, 1H), 9.92 (s, 1H), 7.37 (m, 1H), 7.19 (m, 1H), 7.14 (s, 2H), 2.37 (s, 3H), 2.06 (s, 6H), 1.35 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 196.8, 156.9, 150.4, 139.7, 136.1, 132.9, 132.8, 129.9, 129.1, 124.5, 120.6, 34.5, 31.5, 20.8, 20.5. **IR** (neat, cm^{-1}): 2949, 2863, 1648, 1455, 1322, 1263, 1219, 968, 867. **HRMS** (ESI) *m/z* calculated for $C_{20}H_{25}O_2^+$ ($M + H^+$) 297.1849, found 297.1850.

5-(*Tert*-butyl)-4-hydroxy-2',4',6'-triisopropyl-[1,1'-biphenyl]-3-carbaldehyde (SM10)

4-Bromo-2-(*tert*-butyl)phenol[31] (1.6 g, 7.0 mmol) was added in small portions to a mixture of sodium hydride (Aldrich, 95%, dry, 0.23 g, 9.6 mmol) and THF (7 ml) at 0 °C, followed by stirring at 22 °C for 10 minutes. $Pd(OAc)_2$ (Strem, 0.107 g, 0.351 mmol) was added, followed by 2,4,6-triisopropylphenylmagnesium bromide (Aldrich, 0.5 M, THF, 30 ml, 15 mmol), and the resulting mixture was refluxed for 12 h. Upon cooling to 0 °C, H_2O was carefully added to destroy residual Grignard reagent and

sodium hydride. HCl (2 M, aq.) was added followed by celite, and the resulting mixture was filtered through a pad of celite. The resulting phases were separated and the aqueous phase extracted with Et_2O (3x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was subjected to flash column chromatography. The isolated product (1.88 g) was contaminated with approximately 5% of 2-(*tert*-butyl)phenol, and was used without further purification in the next step. ^{1}H NMR data for the main component, 3-(*tert*-butyl)-2',4',6'-triisopropyl-[1,1'-biphenyl]-4-ol, is provided: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.06 (s, 1H), 7.05 (s, 2H), 6.88–6.85 (m, 1H), 6.68 (d, J = 7.9 Hz, 1H), 4.72 (s, 1H), 2.94 (p, J = 6.9 Hz, 1H), 2.70–2.50 (m, 2H), 1.41 (d, J = 1.3 Hz, 9H), 1.31 (d, J = 6.9 Hz, 6H), 1.09 (d, J = 6.7 Hz, 6H), 1.07 (d, J = 6.8 Hz, 6H).

Methylmagnesium bromide (Acros, 3 M, Et_2O, 2.2 ml, 6.6 mmol) was added slowly to 3-(*tert*-butyl)-2',4',6'-triisopropyl-[1,1'-biphenyl]-4-ol (1.88 g, ca. 5 mmol) in THF (13 ml) at 0 °C. After warming to 22 °C, toluene (26 ml), triethylamine (1.3 ml, 9.3 mmol) and paraformaldehyde (0.42 g, 14 mmol) were added, and the resulting reaction mixture stirred at 80 °C for 12 h. After cooling to 0 °C, H_2O and then HCl (2 M, aq.) were added, and the resulting phases were separated. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography, followed by recrystallization from methanol to give **SM10** (1.32 g, 50% over two steps) as an off-color solid. **MP** 144–143 °C (methanol). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 11.80 (s, 1H), 9.87 (s, 1H), 7.36

(d, *J* = 2.2 Hz, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 7.08 (s, 2H), 2.96 (hept, *J* = 6.9 Hz, 1H), 2.61 (hept, *J* = 6.9 Hz, 2H), 1.43 (s, 9H), 1.32 (d, *J* = 6.9 Hz, 6H), 1.12 (d, *J* = 6.9 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 197.4, 160.0, 148.4, 147.1, 137.9, 136.3, 135.9, 132.4, 131.6, 120.9, 120.4, 35.1, 34.5, 30.5, 29.55, 29.55, 24.5, 24.23, 24.20. **IR** (neat, cm^{-1}): 2958, 2868, 1638, 1436, 1264, 1166, 881, 787. **HRMS** (EI) *m/z* calculated for $C_{26}H_{26}O_2^+$ (M^+) 380.2715, found 380.2709.

2.5.2.3 Synthesis of Salen-Compounds

rac-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-Cyclohexane-1,2-diylbis(azanylylidene))bis(meth-anyly-lidene))bis(2',4',6'-trimethyl-[1,1'-biphenyl]-2-ol) (LF1)

Following general procedure D, 2-hydroxy-2',4',6'-trimethyl-[1,1'-biphenyl]-3-carbaldehyde (**SM5**, 360 mg, 1.50 mmol), *racemic trans*-cyclohexane-1,2-diamine (85.0 mg, 0.744 mmol) and methanol (2.5 ml) were mixed and then stirred at 65 °C for 7 h. Following filtration and drying *in vacuo,* **LF1** (311 mg, 75%) was obtained as a yellow powder. **MP** 184–185 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 13.57 (s, 2H), 8.27 (s, 2H), 7.12 (d, *J* = 6.3 Hz, 2H), 7.06 (d, *J* = 6.2 Hz, 2H), 6.98 (s, 4H), 6.86 (t, *J* = 7.5 Hz, 2H), 3.24 (d, *J* = 9.5 Hz, 2H), 2.36 (s, 6H), 2.06 (s, 6H), 1.98 (d, *J* = 13.4 Hz, 2H), 1.90 (s, 6H), 1.88 (d, *J* = 9.8 Hz, 2H), 1.78–1.60 (m, 2H), 1.46 (t, *J* = 9.9 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.0, 158.2, 136.9, 136.7, 136.5, 134.3, 133.5, 130.5, 128.8, 128.3, 128.2, 118.6, 118.5, 73.0, 32.9, 24.2, 21.3, 20.5, 20.3. **IR** (neat, cm^{-1}): 2933, 2859, 1611, 1441, 1264, 1065, 850, 749. **HRMS** (ESI) *m/z* calculated for $C_{38}H_{43}N_2O_2^+$ ($M + H^+$) 559.3319, found 559.3311.

***rac*-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-Cyclohexane-1,2-diylbis(azanylylidene))bis(meth-anylyli-dene))bis(2',5,6'-trimethyl-[1,1'-biphenyl]-2-ol) (LF2)**

Following general procedure D, 2-hydroxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-carbaldehyde (**SM3**, 359 mg, 1.49 mmol), *racemic trans*-cyclohexane-1,2-diamine (84.0 mg, 0.736 mmol) and ethanol (7 ml) were mixed and then stirred at 80 °C for 7 h. Following filtration and drying *in vacuo,* **LF2** (318 mg, 77%) was obtained as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 13.32 (s, 2H), 8.20 (s, 2H), 7.20–7.13 (m, 6H), 6.91 (s, 2H), 6.88 (s, 2H), 3.21 (d, *J* = 9.6 Hz, 2H), 2.26 (s, 6H), 2.08 (s, 6H), 1.99–1.95 (m, 2H), 1.95 (s, 6H), 1.87 (d, *J* = 8.6 Hz, 2H), 1.69 (q, *J* = 12.1 Hz, 2H), 1.44 (t, *J* = 9.8 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.1, 155.7, 137.4, 136.69, 136.66, 133.9, 130.7, 128.5, 127.42, 127.39, 127.3, 127.2, 118.4, 73.1, 32.9, 24.3, 20.6, 20.43, 20.42. **IR** (neat, cm^{-1}): 2919, 2856, 1628, 1453, 1265, 1151, 1056, 981, 867, 763. **HRMS** (ESI) *m/z* calculated for $C_{38}H_{43}N_2O_2^+$ ($M + H^+$) 559.3319, found 559.3322.

***rac*-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-Cyclohexane-1,2-diylbis(azanylylidene))bis(meth-anylyli-dene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol) (LF3)**

Following general procedure D, 2-hydroxy-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-carbaldehyde (**SM7**, 381 mg, 1.50 mmol), *racemic trans*-cyclohexane-1,2-diamine (83.0 mg, 0.729 mmol) and ethanol (4 ml) were mixed and then stirred at 80 °C for 7 h. Following filtration and drying *in vacuo,* **LF3** (338 mg, 79%) was obtained as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 13.28 (s, 2H), 8.19 (s, 2H), 6.96 (s, 4H), 6.89 (d, *J* = 2.1 Hz, 2H), 6.86 (d, *J* = 2.1 Hz, 2H), 3.19 (d, *J* = 9.7

Hz, 2H), 2.34 (s, 6H), 2.25 (s, 6H), 2.04 (s, 6H), 1.95 (d, *J* = 14.5 Hz, 2H), 1.91 (s, 6H), 1.84 (d, *J* = 8.8 Hz, 2H), 1.70–1.63 (m, 2H), 1.44 (t, *J* = 9.8 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.1, 155.9, 136.8, 136.6, 136.5, 134.4, 134.1, 130.6, 128.6, 128.2, 128.1, 127.3, 118.3, 73.1, 32.9, 24.3, 21.3, 20.6, 20.5, 20.3. **IR** (neat, cm^{-1}): 2918, 2856, 1628, 1599, 1451, 1261, 1105, 981, 849, 794. **HRMS** (ESI) *m/z* calculated for $C_{40}H_{47}N_2O_2^+$ ($M + H^+$) 587.3632, found 587.3646.

3,3''-((1*E*,1'*E*)-(1,2-Phenylenebis(azanylylidene))bis(methanylylidene))-bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol) (LF4)

2-Hydroxy-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-carbaldehyde (**SM7**, 254 mg, 1.00 mmol), benzene-1,2-diamine (54.1 mg, 0.744 mmol) and methanol (5 ml) were mixed and then stirred at 65 °C for 12 h. The reaction mixture was cooled to -20 °C, and the resulting precipitate isolated by filtration, followed by two washings with small amounts of cold methanol to give **LF4** (178 mg, 62%) as an orange powder. **MP** >200 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.76 (s, 2H), 8.59 (s, 2H), 7.32–7.29 (m, 2H), 7.17–7.15 (m, 2H), 7.13 (s, 2H), 6.96 (s, 2H), 6.92 (s, 4H), 2.32 (s, 12H), 1.96 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 164.5, 156.4, 142.7, 136.8, 135.7, 134.3, 131.6, 129.3, 128.10, 128.08, 127.8, 127.5, 120.8, 119.1, 21.3, 20.6, 20.5. **IR** (neat, cm^{-1}): 2916, 1616, 1595, 1447, 1265, 1212, 1108, 981, 848, 754. **HRMS** (ESI) *m/z* calculated for $C_{40}H_{41}N_2O_2^+$ ($M + H^+$) 581.3163, found 581.3156.

3,3''-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol) (LF5)

Following general procedure D, 2-hydroxy-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-carbaldehyde (**SM7**, 254 mg, 0.999 mmol), 2,3-dimethylbutane-2,3-diamine[18] (58.6 mg, 0.504 mmol) and methanol (5 ml) were mixed and then stirred at 65 °C for 7 h. Following filtration and drying *in vacuo,* **LF5** (235 mg, 80%) was obtained as a faint yellow powder. **MP** >200 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 13.74 (s, 2H), 8.31 (s, 2H), 7.01 (d, *J* = 1.7 Hz, 2H), 6.98 (s, 4H), 6.92 (d, *J* = 2.0 Hz, 2H), 2.35 (s, 6H), 2.30 (s, 6H), 2.06 (s, 12H), 1.36 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 162.1, 156.3, 136.8, 136.6, 134.6, 134.3, 131.0, 128.7, 128.2, 127.2, 118.7, 65.3, 23.3, 21.3, 20.6, 20.5. **IR** (neat, cm^{-1}): 2973, 2917, 1622, 1597, 1456, 1378, 1259, 1139, 1101, 975, 848, 832. **HRMS** (ESI) *m/z* calculated for $C_{40}H_{49}N_2O_2^+$ ($M + H^+$) 589.3789, found 589.3779.

3,3''-((1*E*,1'*E*)-((2-Methylpropane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol) (LF6)

Following general procedure D, 2-hydroxy-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-carbaldehyde (**SM7**, 635 mg, 2.50 mmol), 2-methylpropane-1,2-diamine (121.0 mg, 1.37 mmol) and methanol (4 ml) were mixed and then stirred at 65 °C for 12 h. Following filtration and drying *in vacuo,* **LF6** (635 mg, 91%) was obtained as an off-color powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 13.80 (s, 1H), 13.08 (s, 1H), 8.31 (s, 1H), 8.27 (s, 1H), 7.02 (d, *J* = 2.0 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 6.97 (s, 4H), 6.92 (s, 2H), 3.68 (s, 2H), 2.35 (s, 6H), 2.31 (s, 6H), 2.03 (s, 6H), 2.03 (s, 6H),

1.40 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 167.0, 161.8, 156.3, 156.0, 136.9, 136.8, 136.60, 136.56, 134.6, 134.5, 134.4, 134.2, 130.9, 130.8, 128.8, 128.7, 128.3, 128.2, 127.5, 127.3, 118.49, 118.47, 70.8, 60.4, 25.5, 21.26, 21.25, 20.54, 20.52, 20.51, 20.49. **IR** (neat, cm^{-1}): 2975, 2916, 1629, 1602, 1456, 1387, 1263, 1110, 1064, 849. **HRMS** (ESI) *m/z* calculated for $C_{38}H_{45}N_2O_2^+$ ($M + H^+$) 561.3476, found 561.3481.

***rac*-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-Cyclohexane-1,2-diylbis(azanylylidene))bis-(methanylylidene))bis(4'-(*tert*-butyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-2-ol) (LF7)**

Following general procedure D, 4'-(*tert*-butyl)-2-hydroxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-carbaldehyde (**SM9**, 444 mg, 1.50 mmol), *racemic trans*-cyclohexane-1,2-diamine (84.9 mg, 0.743 mmol) and methanol (2.5 ml) were mixed and then stirred at 64 °C for 1 h. Following filtration and drying *in vacuo,* **LF7** (368 mg, 74%) was obtained as a yellow powder. **MP** >200 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.35 (s, 2H), 8.18 (s, 2H), 7.14 (s, 4H), 6.89 (s, 4H), 3.18 (m, 2H), 2.24 (s, 6H), 2.08 (s, 6H), 1.96 (s, 6H), 1.96 (m, 2H), 1.85 (m, 2H), 1.66 (s, 2H), 1.45–1.39 (m, 2H), 1.36 (s, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 165.2, 155.9, 149.8, 136.1, 136.0, 134.4, 134.3, 130.6, 128.7, 127.4, 124.4, 124.3, 118.3, 73.1, 34.4, 32.9, 31.6, 24.3, 21.0, 20.8, 20.4. **IR** (neat, cm^{-1}): 2945, 2861, 122, 1453, 1262, 1097, 862. **HRMS** (ESI) *m/z* calculated for $C_{46}H_{59}N_2O_2^+$ ($M + H^+$) 671.4571, found 671.4574.

The synthesis of (*S*,*S*)- and (*R*,*R*)-**LF7** is analogous to that of the *racemic* compound. **Specific rotation** of (*S*,*S*)-**LF7**: $[\alpha]^{22}_D$ = +425 (*c* = 0.56, $CHCl_3$).

3,3''-((1*E*,1'*E*)-(1,2-Phenylenebis(azanylylidene))bis(methanylylidene))bis(4'-(*tert*-butyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-2-ol) (LF8)

Following general procedure D, 4'-(*tert*-butyl)-2-hydroxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-carbaldehyde (**SM9**, 444 mg, 1.50 mmol), benzene-1,2-diamine (81.1 mg, 0.750 mmol) and methanol (2.5 ml) were mixed and then stirred at 65 °C for 7 h. Following filtration and drying *in vacuo,* **LF8** (336 mg, 67%) was obtained as an orange powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 12.84 (s, 2H), 8.61 (s, 2H), 7.32 (dd, *J* = 5.9, 3.4 Hz, 2H), 7.19 (dd, *J* = 5.8, 3.4 Hz, 2H), 7.16 (d, *J* = 2.0 Hz, 2H), 7.14 (s, 4H), 7.02 (d, *J* = 2.2 Hz, 2H), 2.33 (s, 6H), 2.02 (s, 12H), 1.38 (s, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 164.6, 156.4, 149.7, 142.7, 136.3, 135.9, 134.3, 131.6, 129.4, 127.8, 127.5, 124.3, 120.7, 119.1, 34.4, 31.6, 20.9, 20.5. **IR** (neat, cm^{-1}): 2959, 2865, 1614, 1575, 1445, 1270, 1214, 1097, 861. **HRMS** (ESI) *m/z* calculated for $C_{46}H_{53}N_2O_2^+$ ($M + H^+$) 665.4102, found 665.4122.

***rac*-2,4-Di-*tert*-butyl-6-((*E*)-(((1*S*,2*S*)-2-((3,5-di-*tert*-butyl-2-hydroxybenzyl)(pyridin-2-ylmethyl)amino)cyclohexyl)imino)methyl)phenol (LF9)**

rac-2,4-Di-*tert*-butyl-6-((*E*)-(((1*S*,2*S*)-2-((pyridin-2-ylmethyl)amino)cyclohexyl)-imino)-methyl)phenol[12] (4.95 g, 11.7 mmol), paraformaldehyde (0.42 g, 14.0 mmol), 2,4-di-*tert*-butylphenol (2.41 g, 11.7 mmol), and toluene (13 ml) were mixed in air and stirred at 100 °C for 22 h. Upon cooling to 22 °C, volatiles were removed *in vacuo* and the residue was purified *via* flash column chromatography (using neutral alumina) to afford **LF9** (1.17 g, 16%) as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 13.33 (s, 1H), 10.40 (s, 1H), 8.53–8.45 (m, 1H), 8.33 (s, 1H), 7.70 (td, *J* =

7.7, 1.9 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.18 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 4.19 (d, *J* = 13.5 Hz, 1H), 3.92 (d, *J* = 13.9 Hz, 1H), 3.79 (d, *J* = 13.9 Hz, 1H), 3.56 (d, *J* = 13.5 Hz, 1H), 3.38 (td, *J* = 10.6, 4.3 Hz, 1H), 2.91 (ddd, *J* = 12.8, 10.1, 3.3 Hz, 1H), 2.26 (d, *J* = 12.5 Hz, 1H), 1.91–1.87 (m, 1H), 1.76–1.72 (m, 2H), 1.53 (s, 9H), 1.47–1.33 (m, 4H) 1.30 (s, 9H), 1.27 (s, 9H), 1.09 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 167.0, 158.5, 158.1, 154.1, 148.7, 140.4, 139.8, 137.2, 136.4, 135.7, 126.8, 126.1, 124.3, 124.1, 123.0, 122.4, 121.0, 118.4, 69.9, 63.2, 56.1, 53.3, 35.7, 35.2, 34.8, 34.3, 34.2, 31.8, 31.7, 29.8, 29.5, 25.3, 24.9, 22.4. **IR** (neat, cm^{-1}): 2951, 1629, 1438, 1360, 1238, 986, 878, 756. **HRMS** (ESI) *m/z* calculated for $C_{42}H_{62}N_3O_2^+$ ($M + H^+$) 640.4837, found 640.4839.

2,2'-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(4-methylphenol) (LF10)

Following general procedure D, 2-hydroxy-5-methylbenzaldehyde (204 mg, 1.50 mmol), 2,3-dimethylbutane-2,3-diamine[S18] (87.0 mg, 0.749 mmol), and methanol (4.5 ml) were mixed and then stirred at 70 °C for 11 h. Following filtration and drying *in vacuo,* **LF10** (189 mg, 72%) was obtained as a yellow powder. **MP** 198–199 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 13.81 (s, 2H), 8.32 (s, 2H), 7.11 (dd, *J* = 8.3, 2.2 Hz, 2H), 7.06 (d, *J* = 2.3 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 2.28 (s, 6H), 1.37 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.7, 159.3, 133.1, 131.9, 127.6, 118.7, 116.9, 65.3, 23.2, 20.5. **IR** (neat, cm^{-1}): 2978, 1625, 1590, 1492, 1278, 1133, 822. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{29}N_2O_2^+$ ($M + H^+$) 353.2224, found 353.2225.

6,6'-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(2,4-dimethylphenol) (LF11)

Following general procedure D, 2-hydroxy-3,5-dimethylbenzaldehyde (225 mg, 1.50 mmol), 2,3-dimethylbutane-2,3-diamine[S18] (87.0 mg, 0.749 mmol), and methanol (4.5 ml) were mixed and then stirred at 70 °C for 12 h. Following filtration and drying *in vacuo,* **LF11** (228 mg, 80%) was obtained as a yellow powder. **MP** 178–179 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 14.07 (s, 2H), 8.33 (s, 2H), 7.01 (s, 2H), 6.92 (s, 2H), 2.26 (s, 12H), 1.39 (s, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 161.9, 157.7, 134.4, 129.5, 127.0, 125.8, 117.9, 65.2, 23.3, 20.5, 15.6. **IR** (neat, cm^{-1}): 2971, 2913, 1627, 1601, 1473, 1377, 1264, 1133, 863, 838. **HRMS** (ESI) *m/z* calculated for $C_{24}H_{33}N_2O_2^+$ ($M + H^+$) 381.2537, found 381.2538.

6,6'-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(4-(*tert*-butyl)-2-methylphenol) (LF12)

Following general procedure D, 5-(*tert*-butyl)-2-hydroxy-3-methylbenzaldehyde[29] (384 mg, 2.00 mmol), 2,3-dimethylbutane-2,3-diamine[27] (116 mg, 0.998 mmol), and methanol (6.0 ml) were mixed and then stirred at 70 °C for 8 h. Following filtration and drying *in vacuo,* **LF12** (362 mg, 78%) was obtained as a yellow powder. **MP** 171–173 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 14.1 (s, 2H), 8.40 (s, 2H), 7.23 (s, 2H), 7.12 (s, 2H), 2.30 (s, 6H), 1.40 (s, 12H), 1.31 (s, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 162.2, 157.7, 140.7, 130.9, 125.8, 125.4, 117.5, 65.2, 34.0, 31.6, 23.3, 15.9. **IR** (neat, cm^{-1}): 2965, 1630, 1479, 1380, 1274, 1135, 1040, 979, 861. **HRMS** (ESI) *m/z* calculated for $C_{30}H_{45}N_2O_2^+$ ($M + H^+$) 465.3476, found 465.3471.

5,5''-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(3-(*tert*-butyl)-2',4',6'-triisopropyl-[1,1'-biphenyl]-4-ol) (LF13)

Following general procedure D, **SM10** (381 mg, 1.00 mmol), 2,3-dimethylbutane-2,3-diamine[27] (58 mg, 0.50 mmol), and methanol (15 ml) were mixed and then stirred at 70 °C for 12 h. Following filtration and drying *in vacuo,* **LF13** (319 mg, 76%) was obtained as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 14.51 (s, 2H), 8.45 (s, 2H), 7.14 (d, *J* = 2.1 Hz, 2H), 7.08 (s, 4H), 6.97 (d, *J* = 2.1 Hz, 2H), 2.97 (hept, *J* = 6.9 Hz, 2H), 2.70 (hept, *J* = 6.8 Hz, 4H), 1.47 (s, 12H), 1.45 (s, 18H), 1.33 (d, *J* = 6.9 Hz, 12H), 1.13 (d, *J* = 6.9 Hz, 12H), 1.09 (d, *J* = 6.8 Hz, 12H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 162.5, 159.4, 147.8, 147.2, 137.1, 136.9, 131.5, 130.6, 129.9, 120.7, 118.5, 65.4, 35.1, 34.4, 30.4, 29.7, 24.7, 24.3, 23.5. **IR** (neat, cm^{-1}): 2957, 1630, 1433, 1384, 1267, 1131, 876. **HRMS** (ESI) *m/z* calculated for $C_{58}H_{85}N_2O_2^+$ ($M + H^+$) 841.6606, found 841.6605.

3,3''-((1*E*,1'*E*)-([1,1'-Binaphthalene]-2,2'-diylbis(azanylylidene))bis(methanylylidene))bis(3',5'-di-*tert*-butyl-5-methyl-[1,1'-biphenyl]-2-ol) (BinamSal, LF14)

3',5'-Di-*tert*-butyl-2-hydroxy-5-methyl-[1,1'-biphenyl]-3-carbaldehyde[28] (324 mg, 0.999 mmol), *racemic* [1,1'-binaphthalene]-2,2'-diamine (142 mg, 0.499 mmol) and ethanol (8 ml) were mixed and then refluxed for 12 h. After allowing the reaction mixture to reach 22 °C, the resulting precipitate was isolated by filtration, washed with a small amount of ethanol and finally pentane to give **LF14** (372 mg, 83%) as a powder of orange color. **MP** 196–198 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.36 (s, 2H), 8.62 (s, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 8.8

Hz, 2H), 7.38 (dt, *J* = 8.1, 4.0 Hz, 2H), 7.33 (t, *J* = 1.8 Hz, 2H), 7.26 (d, *J* = 1.8 Hz, 2H), 7.22 (d, *J* = 3.2 Hz, 2H), 7.14 (d, *J* = 2.1 Hz, 2H), 6.92 (d, *J* = 2.2 Hz, 2H), 2.24 (s, 6H), 1.35 (s, 36H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 162.6, 156.2, 150.0, 144.4, 136.6, 135.0, 133.4, 132.5, 131.6, 130.09, 130.05, 129.3, 128.3, 127.6, 127.0, 126.6, 125.8, 123.8, 121.0, 119.4, 117.3, 35.0, 31.8, 20.5. **IR** (neat, cm^{-1}): 2962, 1582, 1462, 1362, 1259, 967, 865, 742, 714. **HRMS** (ESI) *m/z* calculated for $C_{64}H_{69}N_2O_2^+$ ($M + H^+$) 897.5354, found 897.5382.

2.5.2.4 Metallation of Salen-Compounds

6,6'-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(2,4-di-*tert*-butylphenolate)aluminum chloride (MF2, precursor to 1d)

Following general procedure E, Et_2AlCl (Aldrich, hexanes, 1.0 M, 600 µl, 0.600 mmol) was added to 6,6'-((1*E*,1'*E*)-((2,3-dimethylbutane-2,3-diyl)bis(azanylylidene))-bis(methanylylidene))bis(2,4-di-*tert*-butylphenol) (TCI, 277 mg, 0.505 mmol) in DCM (3.0 ml). After stirring at 22 °C, volatiles were removed *in vacuo*. The residue was broken up and further dried *in vacuo* at 80 °C for 1 h to give **MF2** (236 mg, 77%) as a fluorescent yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, C_6D_6): δ 8.04 (s, 2H), 7.84 (s, 2H), 7.15 (s, 2H), 1.88 (s, 18H), 1.39 (s, 18H), 0.96 (s, 6H), 0.53 (s, 6H). **^{13}C NMR** (126 MHz, C_6D_6): δ 167.4, 163.8, 142.0, 138.8, 131.4, 128.1, 119.5, 65.9, 36.2, 34.3, 31.7, 30.4, 24.8, 23.8. **IR** (neat, cm^{-1}): 2952, 1616, 1541, 1472, 1391, 1258, 1153, 854, 756. **HRMS** (ESI) *m/z* calculated for $C_{36}H_{54}AlN_2O_2^+$ $(M - Cl)^+$ 573.3995, found 573.3990.

[Me_4SalAl(THF)$_2$]$^+$[Co(CO)$_4$]$^-$ (1d)

$NaCo(CO)_4$ (33.4 mg, 0.172 mmol), 6,6'-((1*E*,1'*E*)-((2,3-dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(2,4-di-*tert*-butylphenolate)aluminum chloride[S16] (100 mg, 0.164 mmol) and THF (2.5 ml) were mixed and stirred for 12 h at 22 °C. The reaction mixture was filtered through a 0.45 µm teflon syringe filter, the filtrate carefully layered with hexane and then placed in a freezer at -34 °C for a day. The resulting crystals were isolated by filtration, washed with hexanes and then dried *in vacuo* to give **1d** (118 mg, 81%) as yellow crystals. **^{1}H NMR** (400 MHz, C_6D_6): δ 8.75 (s, 2H), 7.87 (d, *J* = 2.6 Hz, 2H), 7.78 (d, *J* = 2.5 Hz, 2H), 3.47–3.23 (m, 8H, THF), 1.65 (s, 18H), 1.43 (s, 18H), 1.18 (s, 12H), 1.20–1.15 (m, 8H, THF). **^{13}C NMR** (126 MHz, C_6D_6 + THF-d8, (1:1, v/v)): δ 171.0, 162.4, 139.4, 132.2, 130.5, 119.9, 67.9, 35.8, 34.5, 31.5, 29.8, 26.3, 25.9. **IR** (neat, cm^{-1}): 2953, 1862 $\nu_{(C=O)}$, 1613, 1401, 1259, 1149, 1019, 848, 760.

***rac*-2,4-Di-*tert*-butyl-6-((*E*)-(((1*S*,2*S*)-2-((3,5-di-*tert*-butyl-2-hydroxybenzyl)(pyridin-2-ylmethyl)amino)cyclohexyl)imino)methyl)phenolaluminum chloride (1e)**

Et_2AlCl (Aldrich, hexanes, 1.0 M, 715 µl, 0.715 mmol) was added to a solution of *rac*-2,4-di-*tert*-butyl-6-((*E*)-(((1*S*,2*S*)-2-((3,5-di-*tert*-butyl-2-hydroxybenzyl)(pyridin-2-ylmethyl)amino)cyclohexyl)imino)methyl)phenol (**LF9**, 352 mg, 0.550 mmol) in DCM (2.5 ml) at 0 °C. The resulting solution was stirred at 22 °C for 24 h, followed by removal of all volatiles *in vacuo*. $NaCo(CO)_4$ (107 mg, 0.552 mmol) and THF (1.5 ml) were added to the residue and stirred for 12 h at 22 °C. The reaction mixture was then filtered through a 0.45 µm teflon syringe filter and concentrated *in vacuo*. The

residue was taken up in a minimum amount of Et_2O and the solution placed in a freezer at -34 °C. The resulting precipitate was isolated by filtration to give **1b** (173 mg, 35%) as a powder of yellow to orange color. The powder can be dissolved in toluene followed by layering with hexanes to give a crystalline yellow solid. No significant difference in terms of activity and selectivity was noted when using the recrystallized species. Catalyst **1e** was stored under nitrogen at -34 °C. **^{1}H NMR** (300 MHz, C_6D_6): δ 8.83 (d, *J* = 4.9 Hz, 1H), 7.97 (s, 1H), 7.83 (d, *J* = 2.6 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.22–7.14 (m, 2H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.46 (t, *J* = 6.7 Hz, 1H), 5.19 (d, *J* = 17.1 Hz, 1H), 3.84 (m, 2H), 3.81 (d, *J* = 16.7 Hz, 1H), 3.31 (d, *J* = 13.4 Hz, 1H), 3.11 (d, *J* = 13.4 Hz, 1H), 2.49 (t, *J* = 10.9 Hz, 1H), 1.87–1.60 (m, 4H), 1.73 (s, 9H), 1.55–1.44 (m, 1H), 1.39 (s, 9H), 1.32 (s, 9H), 1.27 (s, 9H), 0.73–0.58 (m, 1H), 0.25–0.04 (m, 1H). **^{13}C NMR** (126 MHz, C_6D_6): δ 172.6, 162.6, 155.5, 154.9, 147.7, 144.3, 141.2, 140.6, 140.1, 138.6, 133.2, 129.8, 126.1, 125.3, 124.8, 124.7, 120.4, 119.3, 61.6, 59.3, 56.5, 52.8, 35.6, 35.3, 34.4, 34.3, 31.9, 31.4, 30.4, 29.7, 28.8, 24.0, 23.7, 23.2. **IR** (neat, cm^{-1}): 1875 $\nu_{(C=O)}$.

***rac*-6,6'-((1*E*,1'*E*)-((1*S*,2*S*)-Cyclohexane-1,2-diylbis(azanylylidene))bis(methanylylidene))bis(2,4-dimethylphenolate)aluminum chloride (MF1, precursor to 1f)**

Following general procedure E, Et_2AlCl (Aldrich, hexanes, 1.0 M, 520 µl, 0.520 mmol) was added to *rac*-6,6'-((1*E*,1'*E*)-((1*S*,2*S*)-cyclohexane-1,2-diylbis-(azanylylidene))bis(methanylylidene))bis(2,4-dimethylphenol)[25] (174 mg, 0.460 mmol) in DCM (2.0 ml). After stirring at 22 °C, the supernatant was removed *via* filtration, and the residue washed once with 1,4-dioxane. The residue was dried *in*

vacuo at 80 °C for 1 h to give **MF1** (137 mg, 68%) as a yellow powder. **MP** >200 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 1.9 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.18 (s, 2H), 6.92 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 1.8 Hz, 1H), 3.93 (t, *J* = 10.7 Hz, 1H), 3.13 (t, *J* = 11.1 Hz, 1H), 2.55 (d, *J* = 12.0 Hz, 1H), 2.45 (d, *J* = 12.0 Hz, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H), 2.11–2.07 (m, 2H), 1.61–1.38 (m, 4H). The very low solubility of **MF1** in both $CDCl_3$ and C_6D_6 interfered with collection of a ^{13}C NMR spectrum in a reasonable amount of time. **IR** (neat, cm^{-1}): 2946, 1625, 1602, 1557, 1351, 1346, 1265, 1037, 824, 764. **HRMS** (ESI) *m/z* calculated for $C_{24}H_{28}AlN_2O_2^+$ $(M - Cl)^+$ 403.1966, found 403.1964.

rac-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-Cyclohexane-1,2-diylbis(azanylylidene))bis(meth-anyly-lidene))bis(2',4',6'-trimethyl-[1,1'-biphenyl]-2-olate)aluminum chloride (MF4, precursor to 1g)

Following general procedure E, Et_2AlCl (Aldrich, hexanes, 1.0 M, 630 µl, 0.630 mmol) was added to *rac*-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-cyclohexane-1,2-diylbis(aza-nylylidene))bis(methanyly-lidene))bis(2',4',6'-trimethyl-[1,1'-biphenyl]-2-ol) (**LF1**, 311 mg, 0.558 mmol) in DCM (2.5 ml). After stirring at 22 °C, the supernatant was removed *via* filtration, and the residue washed with DCM once. The residue was dried *in vacuo* at 80 °C for 1 h to give **MF4** (292 mg, 84%) as a yellow-white powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.40 (d, *J* = 1.9 Hz, 1H), 8.18 (d, *J* = 2.1 Hz, 1H), 7.30 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.23 (dd, *J* = 5.8, 1.8 Hz, 1H), 7.21 (dd, *J* = 6.2, 1.8 Hz, 1H), 7.17 (dd, *J* = 7.2, 1.9 Hz, 1H), 6.99 (s, 1H), 6.97 (s, 1H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.79 (s, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.61 (s, 1H), 3.87 (t, *J* = 10.7 Hz, 1H),

3.14 (t, *J* = 10.1 Hz, 1H), 2.56 (d, *J* = 11.4 Hz, 1H), 2.50 (s, 3H), 2.46 (d, *J* = 10.7 Hz, 1H), 2.39 (s, 3H), 2.10–2.05 (m, 2H), 2.08 (s, 3H), 1.91 (s, 3H), 1.78 (s, 3H), 1.75 (s, 3H), 1.58–1.38 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 169.0, 164.2, 162.3, 161.6, 138.73, 138.69, 137.9, 137.7, 136.4, 135.52, 135.51, 135.3, 135.1, 134.4, 134.1, 133.42, 133.40, 132.5, 128.20, 128.19, 127.8, 127.7, 119.4, 118.8, 117.3, 116.9, 65.8, 62.3, 28.6, 27.2, 24.1, 23.6, 21.5, 21.5, 21.3, 20.7, 20.2, 19.6. **IR** (neat, cm^{-1}): 2936, 1613, 1556, 1432, 1398, 1232, 1106, 933, 853, 759. **HRMS** (ESI) *m/z* calculated for $C_{38}H_{40}AlN_2O_2^+$ $(M - Cl)^+$ 583.2905, found 583.2906.

***rac*-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-Cyclohexane-1,2-diylbis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-olate)aluminum chloride (MF5, precursor to 1h)**

Following general procedure E, Et_2AlCl (Aldrich, hexanes, 1.0 M, 1.1 ml, 1.1 mmol) was added to *rac*-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-cyclohexane-1,2-diylbis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol) (**LF3**, 587 mg, 1.00 mmol) in DCM (8.0 ml). After stirring at 22 °C, the supernatant was removed *via* filtration, and the residue washed with DCM once. The residue was dried *in vacuo* at 80 °C for 1 h to give **MF5** (362 mg, 56%) as a yellow-white powder. **MP** >200 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 1.9 Hz, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 7.08 (d, *J* = 0.8 Hz, 1H), 7.06 (d, *J* = 2.4 Hz, 1H), 7.00 (s, 2H), 6.98 (s, 1H), 6.96 (s, 1H), 6.79 (s, 1H), 6.59 (s, 1H), 3.87–3.82 (m, 1H), 3.16–3.11 (m, 1H), 2.54 (d, *J* = 13.4 Hz, 1H), 2.50 (s, 3H), 2.47 (d, *J* = 10.6 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H), 2.09 (s, 3H), 2.05 (d, *J* = 21.4 Hz, 2H), 1.93 (s, 3H), 1.79 (s, 3H), 1.77 (s, 3H),

1.57–1.37 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 168.6, 162.4, 162.2, 159.6, 140.2, 139.1, 138.7, 137.6, 136.4, 135.6, 135.4, 135.2, 134.9, 134.5, 133.8, 133.1, 132.6, 132.0, 128.2, 128.1, 127.8, 127.7, 126.0, 125.5, 119.0, 118.4, 65.7, 62.3, 28.6, 27.3, 24.1, 23.6, 21.53, 21.48, 21.2, 20.8, 20.4, 20.3, 20.2, 19.6. **IR** (neat, cm^{-1}): 2950, 2921, 1621, 1557, 1448, 1227, 836, 786. **HRMS** (ESI) *m/z* calculated for $C_{40}H_{44}AlN_2O_2^+$ $(M - Cl)^+$ 611.3218, found 611.3223.

3,3''-((1*E*,1'*E*)-(1,2-Phenylenebis(azanylylidene))bis(methanylylidene))bis-(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-olate)aluminum chloride (MF3, precursor to 1i)

Following general procedure E, Et_2AlCl (Aldrich, hexanes, 1.0 M, 400 µl, 0.400 mmol) was added to 3,3''-((1*E*,1'*E*)-(1,2-phenylenebis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol) (**LF4**, 178 mg, 0.307 mmol) in DCM (4.0 ml). After stirring at 22 °C, the supernatant was removed *via* filtration, and the residue washed with DCM once. The residue was dried *in vacuo* at 80 °C for 1 h to give **MF3** (53.7 mg, 27%) as an orange powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, C_6D_6): δ 8.06 (s, 2H), 7.03 (s, 2H), 7.00 (d, *J* = 2.3 Hz, 2H), 6.96 (s, 2H), 6.89–6.85 (m, 2H), 6.84–6.81 (m, 2H), 6.66 (dd, *J* = 2.3, 1.1 Hz, 2H), 2.53 (s, 6H), 2.32 (s, 6H), 2.09 (s, 6H), 2.08 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 163.2, 161.7, 141.5, 138.2, 137.9, 135.9, 135.6, 135.4, 134.7, 132.9, 128.7, 128.1, 127.9, 126.2, 119.2, 115.7, 21.7, 20.9, 20.7, 20.2. **IR** (neat, cm^{-1}): 2916, 1616, 1551, 1459, 1347, 1214, 833, 752. **HRMS** (ESI) *m/z* calculated for $C_{40}H_{38}AlN_2O_2^+$ $(M - Cl)^+$ 605.2749, found 605.2748.

3,3''-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-olate)aluminum chloride (MF6, precursor to 1j)

Following general procedure E, Et_2AlCl (Aldrich, hexanes, 1.0 M, 450 µl, 0.450 mmol) was added to 3,3''-((1*E*,1'*E*)-((2,3-dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol) (**LF5**, 230 mg, 0.391 mmol) in DCM (6.0 ml). After stirring at 22 °C, volatiles were removed *in vacuo*. The residue was broken up and further dried *in vacuo* at 80 °C for 1 h to give **MF6** (187 mg, 74%) as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 7.03 (d, *J* = 2.5 Hz, 1H), 6.89 (s, 1H), 6.76 (s, 1H), 2.41 (s, 3H), 2.27 (s, 3H), 1.93 (s, 3H), 1.91 (s, 3H), 1.53 (s, 3H), 1.31 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.7, 161.2, 139.7, 138.6, 135.7, 135.5, 135.1, 133.4, 132.4, 128.1, 128.0, 125.7, 119.2, 66.2, 25.4, 24.4, 21.3, 21.2, 20.30, 20.29. **IR** (neat, cm^{-1}): 2913, 1619, 1556, 1461, 1300, 1232, 1155, 829. **HRMS** (ESI) *m/z* calculated for $C_{40}H_{46}AlN_2O_2^+$ $(M - Cl)^+$ 613.3375, found 613.3369.

3,3''-((1*E*,1'*E*)-((2-Methylpropane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-olate)aluminum chloride (MF7, precursor to 1k)

Following general procedure E, Et_2AlCl (Aldrich, hexanes, 1.0 M, 1.1 ml, 1.1 mmol) was added to 3,3''-((1*E*,1'*E*)-((2-methylpropane-1,2-diyl)bis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol) (**LF6**, 561 mg, 1.00 mmol) in DCM (7.5 ml). After stirring at 22 °C, volatiles were removed *in vacuo*.

The residue was broken up and further dried *in vacuo* at 80 °C for 1 h to give **MF7** (597 mg, 96%) as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, C_6D_6): δ 7.80 (s, 1H), 7.47 (s, 1H), 7.10 (s, 1H), 7.00 (s, 1H), 6.98 (dd, *J* = 6.7 Hz, 2.5 Hz, 2H), 6.97 (s, 1H), 6.93 (s, 1H), 6.70 (dd, *J* = 2.4, 1.0 Hz, 1H), 6.63 (d, *J* = 2.2 Hz, 1H), 3.77 (d, *J* = 11.6 Hz, 1H), 2.49 (s, 6H), 2.41 (s, 3H), 2.36 (d, *J* = 12.2 Hz, 1H), 2.30 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 0.86 (s, 3H), 0.46 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.1, 167.4, 162.5, 161.6, 140.1, 139.8, 138.6, 137.9, 136.2, 135.9, 135.7, 135.5, 135.3, 135.2, 134.6, 134.3, 132.6, 131.8, 128.8, 128.40, 128.35, 128.1, 125.6, 125.3, 119.11, 119.07, 65.0, 59.8, 27.6, 24.8, 21.61, 21.59, 21.4, 21.1, 20.7, 20.6, 20.3, 20.2. **IR** (neat, cm^{-1}): 2916, 1621, 1557, 1443, 1277, 1232, 841. **HRMS** (ESI) *m/z* calculated for $C_{38}H_{42}AlN_2O_2^+$ $(M - Cl)^+$ 585.3062, found 585.3062.

rac-3,3''-((1_E_,1'_E_)-((1_S_,2_S_)-Cyclohexane-1,2-diylbis(azanylylidene))bis-(methanylyli-dene))bis(2',5,6'-trimethyl-[1,1'-biphenyl]-2-olate)aluminum chloride (MF8, precursor to 1l)

Following general procedure E, Et_2AlCl (Aldrich, hexanes, 1.0 M, 1.15 ml, 1.15 mmol) was added to *rac*-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-cyclohexane-1,2-diylbis(aza-nylylidene))bis(methanylyli-dene))bis(2',5,6'-trimethyl-[1,1'-biphenyl]-2-ol) (**LF2**, 554 mg, 1.00 mmol) in DCM (7.0 ml). After stirring at 22 °C, the supernatant was removed *via* filtration, and the residue washed with DCM once. The residue was dried *in vacuo* at 80 °C for 1 h to give **MF8** (347 mg, 56%) as a yellow powder. **MP** >200 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ 7.62 (d, *J* = 1.8 Hz, 1H), 7.54 (d, *J* = 2.2 Hz, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.29–7.25 (m, 2H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.19–7.17 (m,

1H), 7.11 (d, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.92 (d, *J* = 2.4 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.71 (d, *J* = 1.8 Hz, 1H), 3.54 (t, *J* = 11.1 Hz, 1H), 2.47 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H), 2.11 (s, 6H), 2.07 (s, 3H), 2.03–2.00 (m, 1H), 1.48–1.43 (m, 2H), 1.36 (d, *J* = 11.3 Hz, 2H), 0.82–0.42 (m, 4H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 168.5, 162.4, 162.1, 159.6, 139.8, 138.8, 138.5, 137.5, 137.3, 136.4, 135.0, 133.8, 133.2, 132.7, 132.1, 127.8, 127.4, 126.9, 126.83, 126.75, 126.6, 126.3, 126.0, 125.6, 118.9, 118.5, 65.7, 62.3, 28.6, 27.3, 24.1, 23.6, 21.5, 20.8, 20.4, 20.3, 20.2, 19.7. **IR** (neat, cm^{-1}): 2959, 1618, 1552, 1443, 1226, 862, 839, 764. **HRMS** (ESI) *m/z* calculated for $C_{38}H_{40}AlN_2O_2^+$ $(M - Cl)^+$ 583.2905, found 583.2907.

rac-3,3''-((1_E_,1'_E_)-((1_S_,2_S_)-Cyclohexane-1,2-diylbis(azanylylidene))bis-(methanylylidene))bis(4'-(_tert_-butyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-2-olate)aluminum chloride (MF9, precursor to 1m)

Following general procedure E, Et_2AlCl (Aldrich, hexanes, 1.0 M, 625 µl, 0.625 mmol) was added to *rac*-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-cyclohexane-1,2-diylbis(azanylylidene))bis-(methanylylidene))bis(4'-(*tert*-butyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-2-ol) (**LF7**, 360 mg, 0.527 mmol) in DCM (2.5 ml). After stirring at 22 °C, the supernatant was removed *via* filtration, and the residue washed with DCM once. The residue was dried *in vacuo* at 80 °C for 1 h to give **MF9** (229 mg, 58%) as a fluorescent yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, C_6D_6): δ 7.70 (s, 1H), 7.67 (s, 1H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.41 (s, 1H), 7.33 (s, 1H), 7.23 (s, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 3.47 (t, *J* = 10.9 Hz, 1H), 2.56 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H), 2.15 (m, 1H),

2.14 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H), 1.56 (s, 9H), 1.55 (s, 9H), 1.55–1.50 (m, 1H), 1.43 (d, J = 10.9 Hz, 1H), 1.32 (d, J = 13.4 Hz, 1H), 1.24 (d, J = 13.2 Hz, 1H), 0.86–0.67 (m, 1H), 0.66–0.53 (m, 1H), 0.53–0.40 (m, 1H), 0.35 (m, 1H). **^{13}C NMR** (126 MHz, C_6D_6): δ 168.6, 163.3, 161.4, 160.4, 149.1, 148.9, 140.1, 139.6, 139.5, 137.8, 136.49, 136.47, 136.0, 135.4, 134.9, 133.8, 132.6, 132.0, 125.9, 125.3, 124.7, 124.6, 124.4, 124.1, 119.9, 118.6, 65.3, 61.8, 34.74, 34.70, 32.1, 32.0, 27.8, 26.6, 23.9, 23.3, 22.2, 21.8, 21.2, 20.33, 20.31, 20.1. **IR** (neat, cm^{-1}): 2966, 1644, 1616, 1552, 1444, 1225, 859, 837. **HRMS** (ESI) *m/z* calculated for $C_{46}H_{56}AlN_2O_2^+$ $(M - Cl)^+$ 695.4152, found 695.4146. **Elemental analysis:** $C_{46}H_{56}AlClN_2O_2$ (731.38), calculated C 75.54, H 7.72 N 3.83; found C 75.39, H 7.73, N 3.84.

The synthesis of (*S*,*S*)- and (*R*,*R*)-**MF9** is analogous to that of the *racemic* compound.

rac-3,3''-((1*E*,1'*E*)-((1*S*,2*S*)-Cyclohexane-1,2-diylbis(azanylylidene))bis-(methanylylidene))bis(4'-(*tert*-butyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-2-olate)aluminum cobaltate (1m)

$NaCo(CO)_4$ (46.4 mg, 0.239 mmol), **MF9** (166 mg, 0.228 mmol) and THF (1.5 ml) were mixed and stirred for 12 h at 22 °C. The reaction mixture was filtered through a 0.45 μm teflon syringe filter, the filtrate carefully layered with hexanes, and then placed in a freezer at -34 °C for one day. The resulting crystals were isolated by filtration, washed with hexanes and then dried *in vacuo* to give **1m** (132 mg, 57%) as yellow crystals. The product was stored under nitrogen at -34 °C. **^{1}H NMR** (500 MHz, C_6D_6): δ 8.24 (s, 2H), 7.47 (s, 2H), 7.20 (s, 2H), 7.13 (s, 2H), 6.87 (s, 2H), 3.17 (s,

2H), 2.49 (d, *J* = 12.1 Hz, 2H), 2.12 (s, 6H), 2.04 (s, 2H), 1.97 (s, 6H), 1.94 (s, 6H), 1.64 (s, 2H), 1.59–1.43 (m, 2H), 1.51 (s, 18H). **^{13}C NMR** (126 MHz, C_6D_6): δ 168.6, 159.9, 149.7, 140.4, 137.5, 136.1, 135.5, 134.0, 132.9, 127.5, 124.6, 124.3, 119.2, 64.9, 34.7, 31.9, 28.1, 24.0, 21.30, 20.2, 20.1. **IR** (neat, cm^{-1}): 2950, 2865, 1866 $\nu_{(C=O)}$, 1621, 1558, 1448, 1231, 1018, 860.

The synthesis of (*S*,*S*)- and (*R*,*R*)-**1m** is analogous to that of the *racemic* compound.

3,3''-((1*E*,1'*E*)-(1,2-Phenylenebis(azanylylidene))bis(methanylylidene))bis(4'-(*tert*-butyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-2-olate)aluminum chloride (MF10, precursor to 1n)

Following general procedure E, Et_2AlCl (Aldrich, hexanes, 1.0 M, 610 µl, 0.610 mmol) was added to 3,3''-((1*E*,1'*E*)-(1,2-phenylenebis(azanylylidene))bis(methanylylidene))bis(4'-(*tert*-butyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-2-ol) (**LF8**, 360 mg, 0.505 mmol) in DCM (2.5 ml). After stirring at 22 °C, the supernatant was removed *via* filtration, and the residue washed with DCM once. The residue was dried *in vacuo* at 80 °C for 1 h to give **MF10** (277 mg, 58%) as an orange powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, C_6D_6): δ 8.07 (s, 2H), 7.45 (d, *J* = 2.0 Hz, 2H), 7.37 (d, *J* = 2.1 Hz, 2H), 6.97 (dd, *J* = 2.4, 0.7 Hz, 2H), 6.85–6.82 (m, 2H), 6.81–6.78 (m, 2H), 6.68 (d, *J* = 2.4 Hz, 2H), 2.38 (s, 6H), 2.13 (s, 6H), 2.07 (s, 6H), 1.58 (s, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 163.1, 161.3, 149.2, 141.6, 138.4, 138.0, 136.1, 135.9, 134.5, 132.8, 127.8, 126.3, 124.6, 124.5, 119.5, 115.7, 34.8, 32.1, 21.4, 20.8, 20.2. **IR** (neat, cm^{-1}):

2965, 1617, 1547, 1455, 1216, 861, 838, 746. **HRMS** (ESI) *m/z* calculated for $C_{46}H_{50}AlN_2O_2^+$ $(M - Cl)^+$ 689.3688, found 689.3689.

6,6'-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(4-(*tert*-butyl)-2-methylphenolate)aluminum chloride (MF11, precursor to 1o)

Following general procedure E, Et_2AlCl (Aldrich, 1.0 M, hexanes, 950 µl, 0.950 mmol) was added to 6,6'-((1*E*,1'*E*)-((2,3-dimethylbutane-2,3-diyl)bis(azanylylidene))-bis(methanylylidene))bis(4-(*tert*-butyl)-2-methylphenol) (**LF12**, 360 mg, 0.775 mmol) in DCM (5.0 ml). After stirring at 22 °C, the volatiles were removed *in vacuo*. The residue was broken up and dried *in vacuo* at 80 °C for 1 h to give **MF11** (276 mg, 68%) as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.45 (s, 2H), 7.42 (d, *J* = 1.5 Hz, 2H), 7.10 (d, *J* = 2.6 Hz, 2H), 2.39 (s, 6H), 1.55 (s, 6H), 1.34 (s, 6H), 1.31 (s, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 167.1, 162.3, 139.3, 135.0, 130.4, 126.7, 117.5, 66.3, 34.0, 31.5, 25.8, 24.4, 16.4. **IR** (neat, cm^{-1}): 2952, 2863, 1618, 1560, 1392, 1275, 1153, 843. **HRMS** (ESI) *m/z* calculated for $C_{30}H_{42}N_2O_2^+$ $(M - Cl)^+$ 489.3056, found 489.3065.

6,6'-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(2,4-dimethylphenolate)aluminum chloride (MF12, precursor to 1p)

Following general procedure E, Et_2AlCl (Aldrich, 1.0 M, hexanes, 750 µl, 0.750 mmol) was added to 6,6'-((1*E*,1'*E*)-((2,3-dimethylbutane-2,3-diyl)bis(azanylylidene))-bis(methanylylidene))bis(2,4-dimethylphenol) (**LF11**, 228 mg, 0.599 mmol) in DCM

(4.0 ml). After stirring at 22 °C, the volatiles were removed *in vacuo*. The residue was broken up and dried *in vacuo* at 80 °C for 1 h to give **MF12** (193 mg, 73%) as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.40 (s, 2H), 7.20 (s, 2H), 6.95 (s, 2H), 2.36 (s, 6H), 2.26 (s, 6H), 1.54 (s, 6H), 1.33 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.8, 162.2, 138.3, 130.7, 130.4, 125.8, 118.1, 66.3, 25.7, 24.3, 20.4, 16.0. **IR** (neat, cm^{-1}): 2973, 1621, 1602, 1556, 1301, 1262, 1156, 1138, 834. **HRMS** (ESI) *m/z* calculated for $C_{24}H_{30}N_2O_2^+$ $(M - Cl)^+$ 405.2117, found 405.2122.

2,2'-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(4-methylphenolate)aluminum chloride (MF13, precursor to 1q)

Following general procedure E, Et_2AlCl (Aldrich, 1.0 M, hexanes, 650 μl, 0.650 mmol) was added to 2,2'-((1*E*,1'*E*)-((2,3-dimethylbutane-2,3-diyl)bis(azanylylidene))-bis(methanylylidene))bis(4-methylphenol) (**LF10**, 188 mg, 0.533 mmol) in DCM (4.0 ml). After stirring at 22 °C, the volatiles were removed *in vacuo*. The residue was broken up and dried *in vacuo* at 80 °C for 1 h to give **MF13** (170 mg, 78%) as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.43 (s, 2H), 7.28 (dd, *J* = 8.7, 2.4 Hz, 2H), 7.15–7.11 (m, 2H), 7.10 (s, 1H), 7.08 (s, 1H), 2.28 (s, 6H), 1.55 (s, 6H), 1.32 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 166.9, 163.4, 137.9, 133.1, 126.6, 122.6, 118.8, 66.5, 25.6, 24.4, 20.3. **IR** (neat, cm^{-1}): 2978, 1624, 1602, 1547, 1390, 1306, 1152, 827. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{26}N_2O_2^+$ $(M - Cl)^+$ 377.1804, found 377.1813.

5,5''-((1*E*,1'*E*)-((2,3-Dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(3-(*tert*-butyl)-2',4',6'-triisopropyl-[1,1'-biphenyl]-4-olate)aluminum chloride (MF14, precursor to 1r)

Following general procedure E, Et_2AlCl (Aldrich, 1.0 M, hexanes, 650 µl, 0.650 mmol) was added to a suspension of 5,5''-((1*E*,1'*E*)-((2,3-dimethylbutane-2,3-diyl)bis(azanylylidene))bis(methanylylidene))bis(3-(*tert*-butyl)-2',4',6'-triisopropyl-[1,1'-biphenyl]-4-ol) (**LF13**, 281 mg, 0.334 mmol) in DCM (7.0 ml). After stirring at 22 °C, the volatiles were removed *in vacuo*. The residue was broken up and dried *in vacuo* at 80 °C for 1 h to give **MF14** (254 mg, 84%) as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.44 (s, 2H), 7.33 (d, *J* = 2.3 Hz, 2H), 7.09 (d, *J* = 4.8 Hz, 4H), 6.99 (d, *J* = 2.2 Hz, 2H), 2.97 (hept, *J* = 6.9 Hz, 2H), 2.79 (p, *J* = 6.9 Hz, 2H), 2.78 (p, *J* = 6.9 Hz, 2H), 1.61 (s, 6H), 1.58 (s, 18H), 1.41 (s, 6H), 1.34 (d, *J* = 6.9 Hz, 12H), 1.17 (d, *J* = 6.9 Hz, 6H), 1.16 (d, *J* = 6.9 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 6H), 1.10 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 167.6, 163.6, 147.9, 147.6, 147.2, 141.4, 136.8, 135.7, 132.3, 129.0, 120.8, 120.6, 119.3, 66.4, 35.7, 34.4, 30.5, 30.4, 30.0, 25.8, 24.79, 24.77, 24.6, 24.33, 24.32, 24.27, 24.25. **IR** (neat, cm^{-1}): 2957, 2866, 1616, 1540, 1409, 1153, 876, 841, 758. **HRMS** (ESI) *m/z* calculated for $C_{58}H_{82}N_2O_2^+$ $(M - Cl)^+$ 865.6186, found 865.6186.

BinamSalAlCl (7b, precursor to 7a)

Following general procedure E, Et_2AlCl (Aldrich, 1.0 M, hexanes, 950 µl, 0.950 mmol) was added to a solution of 3,3''-((1*E*,1'*E*)-([1,1'-binaphthalene]-2,2'-diylbis(azanylylidene))bis(methanylylidene))bis(3',5'di-*tert*-butyl-5-methyl-[1,1'-

biphenyl]-2-ol) (BinamSal, **LF14**, 774 mg, 0.863 mmol) in DCM (8.0 ml) at 0 °C. After stirring at 22 °C for 12 h, approximately half of the solvent was removed *in vacuo*. The remainder was cooled to 0 °C, and the precipitate isolated by filtration. The solid, still kept at 0 °C, was washed with cold DCM, then cold pentane, and subsequently dried *in vacuo* at 80 °C for 1 h to give BinamSalAlCl (**7b**, 549 mg, 66%) as a yellow powder. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$, -55 °C): δ 8.20 (s, 1H), 7.96 (s, 1H), 7.82 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.69–7.67 (m, 2H), 7.62 (s, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.27–7.24 (m, 2H), 7.21 (s, 1H), 7.13 (s, 1H), 7.11–7.03 (m, 4H), 6.98–6.95 (m, 3H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.67 (s, 2H), 1.99 (s, 3H), 1.97 (s, 3H), 1.01 (s, 18H), 0.83 (s, 18H). **^{13}C NMR** (126 MHz, $CDCl_3$, -55 °C): δ 174.1, 168.9, 162.8, 159.3, 149.5, 149.4, 144.2, 143.9, 140.8, 138.9, 136.6, 136.5, 134.0, 133.2, 133.0, 132.45, 132.40, 132.3, 131.8, 131.7, 130.5, 129.4, 128.6, 128.4, 127.2, 127.0, 126.9, 126.8, 126.5, 126.28, 126.25, 126.23, 126.0, 125.9, 125.8, 125.24, 125.22, 124.9, 124.48, 124.45, 124.12, 124.05, 120.6, 120.2, 119.3, 118.7, 34.9, 34.6, 31.5, 31.2, 20.5, 20.4. **IR** (neat, cm^{-1}): 2951, 1582, 1548, 1462, 1259, 1220, 985, 860, 745. **HRMS** (ESI) *m/z* calculated for $C_{64}H_{66}AlN_2O_2^+$ $(M - Cl)^+$ 921.4934, found 921.4906.

2.5.2.5 Regioselective Carbonylation of trans-Epoxides Using Catalyst 1e

rac-(2*R*,3*S*)-Methyl 2-ethyl-3-hydroxybutanoate (5b)

General procedure F was followed using **1e** (27.3 mg, 0.0301 mmol, 7.49 mol %), *rac*-(2*S*,3*S*)-2-ethyl-3-methyloxirane[43] (**2b**, 34.6 mg, 0.402 mmol) and benzene (0.8 ml). The crude reaction mixture was treated with methanol (0.5 ml) and sodium

methoxide (ca. 25.2 mg, ca. 0.466 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **5b** (36.9 mg, 63%) as a colorless oil. The analytical data was in accordance with that reported in the literature.[57] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.98 (q, *J* = 5.7 Hz, 1H), 3.71 (s, 3H), 2.38–2.34 (m, 2H), 1.75–1.63 (m, 2H), 1.18 (d, *J* = 6.2 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 175.7, 68.2, 54.1, 51.7, 20.7, 20.5, 12.3.

***rac*-(3*S*,4*R*)-4-Methyl-3-propyloxetan-2-one (4c)**

Following general procedure F using **1e** (27.3 mg, 0.0301 mmol, 7.34 mol %), *rac*-(2*S*,3*S*)-2-methyl-3-propyloxirane (**2c**, 41.1 mg, 0.413 mmol), and benzene (0.8 ml) gave **4c** (31.5 mg, 60%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.74 (p, *J* = 6.4 Hz, 1H), 3.61 (ddd, *J* = 8.6, 7.6, 6.3 Hz, 1H), 1.81–1.72 (m, 1H), 1.64–1.36 (m, 3H), 1.46 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.1, 71.8, 52.7, 26.0, 20.8, 15.8, 14.0. **IR** (neat, cm^{-1}): 2961, 2875, 1808, 1387, 1288, 1120, 1019, 823. **HRMS** (ESI) *m/z* calculated for $C_7H_{13}O_2^+$ ($M + H^+$) 129.0910, found 129.0920.

***rac*-(3*S*,4*R*)-3-Butyl-4-methyloxetan-2-one (4d)**

Following general procedure F using **1e** (27.3 mg, 0.0301 mmol, 7.60 mol %), *rac*-(2*S*,3*S*)-2-butyl-3-methyloxirane[44] (**2d**, 45.2 mg, 0.396 mmol), and benzene (0.8 ml) gave **4d** (36.7 mg, 65%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.73 (p, *J* = 6.4 Hz, 1H), 3.58 (td, *J* = 8.2, 6.3 Hz, 1H), 1.81–1.73 (m, 1H), 1.64–1.57 (m, 1H),

1.51–1.42 (m, 1H), 1.45 (d, J = 6.4 Hz, 3H), 1.39–1.30 (m, 3H), 0.91 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.2, 71.9, 52.9, 29.6, 23.7, 22.6, 15.7, 13.9. **IR** (neat, cm^{-1}): 2958, 2864, 1809, 1463, 1387, 1285, 1120, 1019, 821. **HRMS** (EI) *m/z* calculated for $C_8H_{14}O_2^+$ (M^+) 142.0988, found 142.0990.

***rac*-(3*S*,4*R*)-4-Methyl-3-pentyloxetan-2-one (4a)**

Following general procedure F using **1e** (26.3 mg, 0.0290 mmol, 7.58 mol %), *rac*-(2*S*,3*S*)-2-methyl-3-pentyloxirane[44] (**2a**, 49.0 mg, 0.382 mmol), and benzene (0.8 ml) gave **4a** (40.3 mg, 68%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.74 (p, J = 6.4 Hz, 1H), 3.59 (ddd, J = 8.6, 7.8, 6.3 Hz, 1H), 1.82–1.72 (m, 1H), 1.65–1.55 (m, 1H), 1.54–1.43 (m, 1H), 1.45 (d, J = 6.4 Hz, 3H), 1.42–1.25 (m, 5H), 0.89 (t, J = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.2, 71.9, 53.0, 31.6, 27.2, 24.0, 22.5, 15.8, 14.1. **IR** (neat, cm^{-1}): 2932, 2861, 1812, 1460, 1386, 1286, 1120, 1020, 824. **HRMS** (ESI) *m/z* calculated for $C_9H_{17}O_2^+$ ($M + H^+$) 157.1223, found 157.1236.

***rac*-(3*S*,4*R*)-3-Hexyl-4-methyloxetan-2-one (4e)**

Following general procedure F using **1e** (27.3 mg, 0.0301 mmol, 7.48 mol %), *rac*-(2*S*,3*S*)-2-hexyl-3-methyloxirane[44] (**2e**, 57.0 mg, 0.401 mmol) and benzene (0.8 ml) gave **4e** (48.5 mg, 71%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.74 (p, J = 6.4 Hz, 1H), 3.59 (ddd, J = 8.5, 7.8, 6.4 Hz, 1H), 1.82–1.73 (m, 1H), 1.65–1.56 (m, 1H), 1.53–1.42 (m, 1H), 1.46 (d, J = 6.4 Hz, 3H), 1.39–1.25 (m, 7H), 0.87 (t, J = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.2, 71.9, 52.9, 31.6, 29.1, 27.4, 24.0, 22.7, 15.8, 14.1. **IR** (neat, cm^{-1}): 2929, 2859, 1813, 1460, 1386, 1285, 1120, 1020,

823. **HRMS** (ESI) *m/z* calculated for $C_{10}H_{18}O_2Na^+$ (M + Na^+) 193.1199, found 193.1209.

2.5.2.6 Regioselective Carbonylation of trans-Epoxides using Catalyst 1m

rac-(2*R*,3*S*)-Methyl 3-hydroxy-2-methylpentanoate (6b)

General procedure G was followed using **1m** (11.4 mg, 0.0156 mmol, 5.15 mol %), $NaCo(CO)_4$ (THF, 0.05 M, 320 µl, 0.0160 mmol, 5.28 mol %), and *rac*-(2*S*,3*S*)-2-ethyl-3-methyloxirane[43] (**2b**, THF, 1.01 M, 300 µl, 0.303 mmol). The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 19.0 mg, ca. 0.352 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **6b** (26.6 mg, 60%) as a yellow oil. The analytical data was in accordance with that reported in the literature.[58] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.80 (tt, *J* = 8.5, 4.0 Hz, 1H), 3.69 (s, 3H), 2.65–2.38 (m, 2H), 1.62–1.34 (m, 2H), 1.16 (d, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.7, 73.4, 51.9, 44.0, 26.9, 10.7, 10.5.

rac-(2*R*,3*S*)-Methyl 3-hydroxy-2-methylhexanoate (6c)

General procedure G was followed using **1m** (7.3 mg, 0.010 mmol, 5.1 mol %), $NaCo(CO)_4$ (THF, 0.05 M, 200 µl, 0.0100 mmol, 5.05 mol %) and *rac*-(2*S*,3*S*)-2-methyl-3-propyloxirane (**2c**, THF, 0.992 M, 200 µl, 0.198 mmol). The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **6c** (21.8 mg, 68%) as a colorless oil. The analytical data was in accordance with that reported in the literature.[59] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.91–3.87 (m, 1H), 3.70 (d, *J* = 1.3 Hz, 3H), 2.52 (qd, *J* = 7.2, 3.6, Hz, 1H), 2.49 (d, *J* = 4.6 Hz, 1H), 1.56–1.40 (m, 2H),

1.39–1.28 (m, 2H), 1.18 (d, J = 7.2 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.8, 71.6, 51.9, 44.3, 36.1, 19.3, 14.1, 10.8.

***rac*-(2*R*,3*S*)-Methyl 3-hydroxy-2-methylheptanoate (6d)**

General procedure G was followed using **1m** (7.3 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (THF, 0.05 M, 200 µl, 0.0100 mmol, 5.00 mol %) and *rac*-(2*S*,3*S*)-2-butyl-3-methyloxirane[44] (**2d**, THF, 1.00 M, 200 µl, 0.200 mmol). The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **6d** (25.7 mg, 74%) as a colorless oil. The analytical data was in accordance with that reported in the literature.[26] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.87 (dt, J = 8.3, 4.1 Hz, 1H), 3.69 (s, 3H), 2.55–2.50 (m, 2H), 1.49–1.24 (m, 6H), 1.17 (d, J = 7.2 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.8, 71.9, 51.9, 44.3, 33.6, 28.3, 22.7, 14.1, 10.7.

***rac*-(2*R*,3*S*)-Methyl 3-hydroxy-2-methyloctanoate (6a)**

General procedure G was followed using **1m** (7.3 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (THF, 0.05 M, 200 µl, 0.0100 mmol, 5.00 mol %) and *rac*-(2*S*,3*S*)-2-methyl-3-pentyloxirane[44] (**2a**, THF, 0.998 M, 200 µl, 0.200 mmol). The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **6a** (29.8

mg, 79%) as a colorless oil. The analytical data was in accordance with that reported in the literature.[60] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.88 (dq, *J* = 8.3, 4.1 Hz, 1H), 3.70 (s, 3H), 2.54 (qd, *J* = 7.2, 3.5 Hz, 1H), 2.48 (d, *J* = 4.4 Hz, 1H), 1.50–1.42 (m, 2H), 1.40–1.24 (m, 6H), 1.18 (d, *J* = 7.3 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.8, 71.9, 51.9, 44.3, 33.9, 31.9, 25.8, 22.7, 14.2, 10.7.

***rac*-(2*R*,3*S*)-Methyl 3-hydroxy-2-methylnonanoate (6e)**

General procedure G was followed using **1m** (7.3 mg, 0.010 mmol, 4.9 mol %), $NaCo(CO)_4$ (THF, 0.05 M, 200 µl, 0.0100 mmol, 4.85 mol %), *rac*-(2*S*,3*S*)-2-hexyl-3-methyloxirane[44] (**2e**, 29.3 mg, 0.206 mmol) and THF (0.2 ml). The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **6e** (35.6 mg, 85%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.87 (ddd, *J* = 8.3, 4.4, 3.4 Hz, 1H), 3.70 (s, 3H), 2.55–2.50 (broad s, 1H), 2.52 (tt, *J* = 7.2, 3.6 Hz, 1H), 1.49–1.41 (m, 2H), 1.40–1.21 (m, 8H), 1.17 (d, *J* = 7.2 Hz, 3H), 0.88–0.85 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.8, 71.9, 51.9, 44.3, 33.9, 31.9, 29.3, 26.1, 22.7, 14.2, 10.7. **IR** (neat, cm^{-1}): 3444, 2930, 2857, 1736, 1458, 1198, 1166, 1037. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{22}NaO_3^+$ ($M + Na^+$) 225.1461, found 225.1471.

***rac*-(2*R*,3*S*)-Methyl 6-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-methylhexanoate (6f)**

General procedure G was followed using **1m** (7.3 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (THF, 0.05 M, 200 µl, 0.0100 mmol, 5.00 mol %) and *rac-tert*-butyldimethyl(3-((2*S*,3*S*)-3-methyloxiran-2-yl)propoxy)silane (**2f**, THF, 0.998 M, 200 µl, 0.200 mmol). The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **6f** (43.5 mg, 75%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.86 (dq, *J* = 8.3, 4.1 Hz, 1H), 3.69 (s, 3H), 3.65 (t, *J* = 5.7 Hz, 2H), 3.09 (d, *J* = 4.3 Hz, 1H), 2.54 (qd, *J* = 7.1, 4.4 Hz, 1H), 1.71–1.45 (m, 4H), 1.19 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.5, 71.9, 63.3, 51.8, 44.8, 31.3, 29.4, 26.0, 18.4, 11.4, -5.2. **IR** (neat, cm^{-1}): 2952, 2857, 1737, 1254, 1094, 833, 774. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{31}O_4Si^+$ ($M + H^+$) 291.1986, found 291.1994.

***rac*-(2*R*,3*S*)-Methyl 5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-methylpentanoate (6g)**

General procedure G was followed using **1m** (11.0 mg, 0.0150 mmol, 7.30 mol %), $NaCo(CO)_4$ (THF, 0.05 M, 300 µl, 0.0150 mmol, 7.28 mol %), *rac-tert*-butyldimethyl(2-((2*S*,3*S*)-3-methyloxiran-2-yl)ethoxy)silane (**2g**, 44.6 mg, 0.206 mmol) and THF (100 µl). The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22

°C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **6g** (46.4 mg, 81%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.06–4.02 (m, 1H), 3.87 (ddd, *J* = 10.2, 5.7, 4.5 Hz, 1H), 3.80 (ddd, *J* = 10.2, 8.1, 4.1 Hz, 1H), 3.68 (s, 3H), 3.52 (d, *J* = 2.9 Hz, 1H), 2.54 (qd, *J* = 7.1, 5.4 Hz, 1H), 1.72–1.65 (m, 1H), 1.63–1.57 (m, 1H) 1.21 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.0, 72.2, 62.3, 51.8, 45.3, 36.0, 26.0, 18.3, 12.1, -5.4. **IR** (neat, cm^{-1}): 3497, 2953, 2857, 1737, 1253, 1081, 832, 775. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{29}O_4Si^+$ ($M + H^+$) 271.1830, found 277.1835.

***rac*-(3*R*,4*R*)-4-(((*Tert*-butyldimethylsilyl)oxy)methyl)-3-methyloxetan-2-one (3h)**

General procedure G was followed using **1m** (14.6 mg, 0.0200 mmol, 9.85 mol %), $NaCo(CO)_4$ (THF, 0.05 M, 400 µl, 0.0200 mmol, 9.85 mol %) and *rac-tert*-butyldimethyl(((2*S*,3*S*)-3-methyloxiran-2-yl)methoxy)silane[46] (**2h**, 41.0 mg 0.203 mmol). The crude reaction mixture was concentrated under reduced pressure and then subjected to flash column chromatography to give **3h** (43.0 mg, 92%) as a colorless liquid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.52 (dt, *J* = 6.7, 4.9 Hz, 1H), 3.97–3.90 (m, 2H), 3.81–3.75 (m, 1H), 1.34 (d, *J* = 7.7 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.4, 74.0, 61.3, 47.2, 25.9, 18.3, 8.3, -5.35, -5.42. **IR** (neat, cm^{-1}): 2930, 2858, 1823, 1463, 1253, 1104, 1016, 829, 776. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{23}O_3Si^+$ ($M + H^+$) 231.1411, found 231.1418.

***rac*-(3*R*,4*S*)-4-Benzyl-3-methyloxetan-2-one (3i)**

General procedure G was followed using **1m** (7.3 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (THF, 0.05 M, 200 µl, 0.0100 mmol, 4.95 mol %) and *rac*-(2*S*,3*S*)-2-benzyl-3-methyloxirane (**2i**, THF, 1.01 M, 200 µl, 0.202 mmol). The crude reaction mixture was concentrated under reduced pressure and then subjected to flash column chromatography to give **3i** (29.5 mg, 84%) as an off-white solid. **MP** 60–62 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35–7.30 (m, 2H), 7.28–7.2 (m, 3H), 4.80 (ddd, *J* = 8.8, 6.3, 5.0 Hz, 1H), 3.82 (qd, *J* = 7.8, 6.3 Hz, 1H), 3.12 (dd, *J* = 14.8, 8.8 Hz, 1H), 2.99 (dd, *J* = 14.8, 5.0 Hz, 1H), 1.37 (d, *J* = 7.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.3, 136.1, 129.0, 128.9, 127.1, 75.8, 47.8, 36.4, 8.5. **IR** (neat, cm^{-1}): 2968, 1808, 1454, 1382, 1263, 1146, 1014, 830, 701. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{13}O_2^+$ ($M + H^+$) 177.0910, found 177.0917.

2.5.2.7 Regioselective Carbonylation of cis-Epoxides Using Catalyst 1d

***rac*-(3*R*,4*R*)-4-Ethyl-3-methyloxetan-2-one (10b) and *rac*-(3*R*,4*R*)-4-methyl-3-propyloxetan-2-one (11b)**

General procedure H was followed using **1d** (18.6 mg, 0.0209 mmol, 7.21 mol %), THF (0.6 ml), and *rac*-(2*S*,3*R*)-2-ethyl-3-methyloxirane[48] (**9b**, 25.0 mg, 0.290 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to bulb-to-bulb distillation to give a mixture of **10b** and **11b** (22.0 mg, 66%) as a yellow oil. Analytical data for **10b**[61] and **11b**[62] has previously been reported. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.41 (qd, *J* = 6.1, 4.0 Hz, 1H, **11b**), 4.13 (td, *J* = 6.6, 4.0 Hz, 1H, **10b**), 3.22 (qd, *J* = 7.5, 4.0 Hz, 1H, **10b**), 3.13 (ddd, *J* = 8.4, 6.7, 4.0 Hz, 1H, **11b**),

1.94–1.73 (m, 4H), 1.55 (d, J = 6.1 Hz, 3H, **11b**), 1.39 (d, J = 7.5 Hz, 3H, **10b**), 1.03 (t, J = 7.5 Hz, 3H, **10b**), 1.00 (t, J = 7.6 Hz, 3H, **11b**). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.1 (**10b**), 171.2 (**11b**), 80.6 (**10b**), 74.2 (**11b**), 59.0 (**11b**), 50.4 (**10b**), 27.3 (**10b**), 21.0 (**11b**), 20.4 (**11b**), 12.7 (**10b**), 11.2 (**11b**), 9.1 (**10b**).

***rac*-(3*R*,4*R*)-3-Methyl-4-propyloxetan-2-one (10c) and *rac*-(3*R*,4*R*)-3-ethyl-4-methyloxetan-2-one (11c)**

General procedure H was followed using **1d** (18.6 mg, 0.0209 mmol, 6.74 mol %), THF (0.6 ml), and *rac*-(2*R*,3*S*)-2-methyl-3-propyloxirane[48] (**9c**, 31.0 mg, 0.310 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to flash column chromatography to give a mixture of **10c** and **11c** (22.0 mg, 66%) as a yellow oil. Analytical data for **10c**[61] and **11c**[63] has previously been reported. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.40 (qd, J = 6.1, 3.9 Hz, 1H, **11c**), 4.18 (ddd, J = 7.3, 6.2, 4.0 Hz, 1H, **10c**), 3.24–3.14 (m, 2H), 1.89–1.78 (m, 2H), 1.76–1.65 (m, 2H), 1.55 (d, J = 6.1 Hz, 3H, **11c**), 1.50–1.34 (m, 4H), 1.38 (d, J = 7.5 Hz, 3H, **10c**), 0.98 (t, J = 7.5 Hz, 3H, **10c**), 0.95 (t, J = 7.3 Hz, 3H, **11c**). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.2 (**10c**), 171.4 (**11c**), 79.5 (**10c**), 74.7 (**11c**), 57.5 (**11c**), 50.8 (**10c**), 36.2 (**10c**), 29.8 (**11c**), 20.4 (**11c**), 20.3 (**11c**), 18.5 (**10c**), 13.80 (**10c**), 13.79 (**11c**), 12.6 (**10c**).

***rac*-(3*R*,4*R*)-4-Butyl-3-methyloxetan-2-one (10a) and *rac*-(3*R*,4*R*)-3-butyl-4-methyloxetan-2-one (11a)**

General procedure H was followed using **1d** (13.3 mg, 0.0150 mmol, 4.93 mol %), THF (0.6 ml), and *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane[49] (**9a**, 34.7 mg, 0.304

mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to flash column chromatography to give a mixture of **10a** and **11a** (34.7 mg, 80%) as a colorless oil. Analytical data for **10a**[61] and **11a**[48] has previously been reported. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.38 (qd, *J* = 6.1, 4.0 Hz, 1H, **11a**), 4.15 (ddd, *J* = 7.2, 6.3, 4.0 Hz, 1H, **10a**), 3.20 (qd, *J* = 7.5, 4.0 Hz, 1H, **10a**), 3.17–3.12 (m, 1H, **11a**), 1.90–1.68 (m, 2H + 2H, **10a** + **11a**), 1.53 (d, *J* = 6.1 Hz, 3H, **11a**), 1.37 (d, *J* = 7.5 Hz, 3H, **10a**), 1.48–1.26 (m, 4H + 4H, **10a** + **11a**), 0.93–0.88 (m, 3H + 3H, **10a** + **11a**). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.2 (**10a**), 171.5 (**11a**), 79.7 (**10a**), 74.7 (**11a**), 57.7 (**11a**), 50.8 (**10a**), 33.9 (**10a**), 29.1 (**11a**), 27.5 (**11a**), 27.2 (**10a**), 22.5 (**11a**), 22.4 (**10a**), 20.4 (**11a**), 14.0 (**10a**), 13.9 (**11a**), 12.6 (**10a**).

***rac*-(3*R*,4*R*)-3-Methyl-4-pentyloxetan-2-one (10d) and *rac*-(3*R*,4*R*)-4-methyl-3-pentyloxetan-2-one (11d)**

General procedure H was followed using **1d** (17.8 mg, 0.0200 mmol, 6.58 mol %), THF (0.6 ml), and *rac*-(2*R*,3*S*)-2-methyl-3-pentyloxirane[48] (**9d**, 39.0 mg, 0.304 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to flash column chromatography to give a mixture of **10d** and **11d** (35.2 mg, 74%) as a colorless oil. Analytical data for **10d**[64] and **11d**[48] has previously been reported. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.38 (qd, *J* = 6.1, 3.9 Hz, 1H, **11d**), 4.16 (td, *J* = 6.7, 4.0 Hz, 1H, **10d**), 3.20 (qd, *J* = 7.6, 4.0 Hz, 1H, **10d**), 3.16 (ddd, *J* = 8.9, 6.5, 3.9 Hz, 1H, **11d**), 1.89–1.79 (m, 2H), 1.78–1.6 (m, 2H), 1.54 (d, *J* = 6.0 Hz, 3H, **11d**), 1.48–1.24 (m, 12H), 1.38 (d, *J* = 7.5 Hz, 3H, **10d**), 0.90–0.86 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.2 (**10d**), 171.5 (**11d**), 79.7 (**10d**), 74.8 (**11d**), 57.7 (**11d**), 50.8 (**10d**),

34.2 (**10d**), 31.50 (**11d**), 31.46 (**10d**), 27.7 (**11d**), 26.6 (**11d**), 24.7 (**10d**), 22.54 (**10d**), 22.46 (**11d**), 20.4 (**11d**), 14.04 (**11d**), 14.02 (**10d**), 12.6 (**10d**).

***rac*-(3*R*,4*R*)-4-Hexyl-3-methyloxetan-2-one (10e) and *rac*-(3*R*,4*R*)-3-hexyl-4-methyloxetan-2-one (11e)**

General procedure H was followed using **1d** (13.3 mg, 0.0150 mmol, 5.02 mol %), THF (0.6 ml), and *rac*-(2*S*,3*R*)-2-hexyl-3-methyloxirane[48] (**9e**, 42.5 mg, 0.299 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to flash column chromatography to give a mixture of **10e** and **11e** (48.3 mg, 95%) as a colorless oil. Analytical data for **10e**[65] and **11e**[48] has previously been reported. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.38 (qd, *J* = 6.1, 4.0 Hz, 1H, **11e**), 4.15 (td, *J* = 6.6, 3.9 Hz, 1H, **10e**), 3.20 (qd, *J* = 7.5, 4.0 Hz, 1H, **10e**), 3.14 (ddd, *J* = 8.9, 6.5, 3.9 Hz, 1H, **11e**), 1.88–1.78 (m. 2H), 1.78–1.65 (m. 2H), 1.54 (d, *J* = 6.1 Hz, 3H), 1.47–1.21 (m, 16H), 1.37 (d, *J* = 7.6 Hz, 3H), 0.89–0.85 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.2 (**10e**), 171.5 (**11e**), 79.7 (**10e**), 74.7 (**11e**), 57.7 (**11e**), 50.8 (**10e**), 34.2 (**10e**), 31.7 (**10e**), 31.6 (**11e**), 29.00 (**11e**), 28.96 (**10e**), 27.8 (**11e**), 26.9 (**11e**), 25.0 (**10e**), 22.60 (**11e**), 22.57 (**10e**), 20.4 (**11e**), 14.11 (**11e**), 14.11 (**10e**), 12.6 (**10e**).

***rac*-(3*R*,4*R*)-4-(Cyclohexylmethyl)-3-methyloxetan-2-one (10f) and *rac*-(3*R*,4*R*)-3-(cyclohexylmethyl)-4-methyloxetan-2-one (11f)**

General procedure H was followed using **1d** (8.9 mg, 0.0100 mmol, 4.98 mol %), THF (0.4 ml), and (2*S*,3*R*)-2-(cyclohexylmethyl)-3-methyloxirane (**9f**, 31.0 mg, 0.201 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to

flash column chromatography to give a mixture of **10f** and **11f** (32.3 mg, 88%) as a colorless oil. Only analytical data for **10f** is provided: **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.28–4.23 (m, 1H), 3.23–3.14 (m, 1H), 1.83–1.53 (m, 7H), 1.39 (d, *J* = 7.6 Hz, 3H), 1.50–1.34 (m, 1H), 1.32–1.12 (m, 3H), 1.08–0.89 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.3, 78.4, 51.3, 42.0, 34.9, 33.5, 33.1, 26.4, 26.2, 26.1, 12.6. **IR** (neat, cm^{-1}): 2922, 2851, 1818, 1449, 1125, 947, 859, 806. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{19}O_2^+$ ($M + H^+$) 183.1380, found 183.1390.

***rac*-(3*R*,4*R*)-4-Benzyl-3-methyloxetan-2-one (10g) and *rac*-(3*R*,4*R*)-3-benzyl-4-methyloxetan-2-one (11g)**

General procedure H was followed using **1d** (13.2 mg, 0.0148 mmol, 7.33 mol %), THF (0.4 ml), (2*S*,3*R*)-2-benzyl-3-methyloxirane (**9g**, 30.0 mg, 0.202 mmol). After stirring at 22 °C for 21 h, the crude reaction mixture was subjected to flash column chromatography to give a mixture of **10g** and **11g** (31.8 mg, 90%) as a colorless oil. Only analytical data for **10g** is provided: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36–7.27 (m, 3H), 7.23–7.20 (m, 2H), 4.40 (td, *J* = 6.5, 4.0 Hz, 1H), 3.33 (qd, *J* = 7.5, 4.0 Hz, 1H), 3.20 (dd, *J* = 14.2, 6.4 Hz, 1H), 3.04 (dd, *J* = 14.3, 6.5 Hz, 1H), 1.30 (d, *J* = 7.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.6, 135.3, 129.2, 128.9, 127.3, 79.0, 50.5, 40.1, 12.5. **IR** (neat, cm^{-1}): 3030, 2936, 1816, 1455, 1125, 1053, 884, 812, 699. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{13}O_2^+$ ($M + H^+$) 177.0910, found 177.0919.

***rac*-(3*R*,4*R*)-3-Methyl-4-phenethyloxetan-2-one (10h) and *rac*-(3*R*,4*R*)-4-methyl-3-phenethyloxetan-2-one (11h)**

General procedure H was followed using **1d** (13.2 mg, 0.0149 mmol, 7.30 mol %), THF (0.4 ml), and (2*R*,3*S*)-2-methyl-3-phenethyloxirane (**9h**, 33.1 mg, 0.204 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to flash column chromatography to give a mixture of **10h** and **11h** (33.5 mg, 86%) as a colorless oil. Analytical data for **10h** has previously been reported in the literature.[66] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.33–7.30 (m, 2H + 2H, **10h** + **11h**), 7.25–7.19 (m, 3H + 3H, **10h** + **11h**), 4.32 (qd, *J* = 6.1, 3.9 Hz, 1H, **11h**), 4.17 (ddd, *J* = 7.7, 5.8, 3.9 Hz, 1H, **10h**), 3.20 (qd, *J* = 7.5, 4.0 Hz, 1H, **10h**), 3.15 (ddd, *J* = 9.1, 6.5, 4.0 Hz, 1H, **11h**), 2.83 (ddd, *J* = 14.2, 8.8, 5.5 Hz, 1H + 1H, **10h** + **11h**), 2.71 (dt, *J* = 13.9, 8.0 Hz, 1H + 1H, **10h** + **11h**), 2.23–2.16 (m, 1H + 1H, **10h** + **11h**), 2.12–2.05 (m, 1H + 1H, **10h** + **11h**), 1.43 (d, *J* = 6.1 Hz, 3H, **11h**), 1.33 (d, *J* = 7.6 Hz, 3H, **10h**). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.9 (**10h**), 171.2 (**11h**), 140.2 (**11h**), 140.1 (**10h**), 128.67 (**10h**), 128.66 (**11h**), 128.5 (**11h**), 128.4 (**10h**), 126.5 (**11h**), 126.4 (**10h**), 78.7 (**10h**), 75.0 (**11h**), 56.8 (**11h**), 50.9 (**10h**), 35.8 (**10h**), 33.1 (**11h**), 31.3 (**10h**), 29.5 (**11h**), 20.1 (**11h**), 12.5 (**10h**). **IR** (neat, cm^{-1}): 3027, 2935, 1816, 1455, 1386, 1125, 841, 747, 699. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{15}O_2^+$ ($M + H^+$) 191.1067, found 191.1080.

***rac*-(3*R*,4*R*)-4-Isopentyl-3-methyloxetan-2-one (10i) and *rac*-(3*R*,4*R*)-3-isopentyl-4-methyloxetan-2-one (11i)**

General procedure H was followed using **1d** (13.2 mg, 0.0149 mmol, 5.16 mol %), THF (0.6 ml), and *rac*-(2*S*,3*R*)-2-isopentyl-3-methyloxirane[48] (**9i**, 37.0 mg, 0.289

mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to flash column chromatography to give a mixture of **10i** and **11i** (40.9 mg, 91%) as a colorless oil. Analytical data for **10i** and **11i** has previously been reported in the literature.[48] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.39 (qd, *J* = 6.1, 3.9 Hz, 1H, **11i**), 4.13 (td, *J* = 6.7, 4.0 Hz, 1H, **10i**), 3.21 (qd, *J* = 7.5, 4.0 Hz, 1H, **10i**), 3.12 (ddd, *J* = 8.9, 6.5, 3.9 Hz, 1H, **11i**), 1.88–1.80 (m, 2H), 1.78–1.69 (m, 2H), 1.62–1.51 (m, 2H), 1.55 (d, *J* = 6.2 Hz, 3H, **11i**), 1.38 (d, *J* = 7.5 Hz, 3H, **10i**), 1.35–1.28 (m, 2H), 1.25–1.16 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H, **11i**), 0.89 (d, *J* = 6.6 Hz, 6H, **10i**). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.2 (**10i**), 171.5 (**11i**), 79.9 (**10i**), 74.7 (**11i**), 57.8 (**11i**), 50.8 (**10i**), 35.9 (**11i**), 33.9 (**10i**), 32.2 (**10i**), 27.92 (**11i**), 27.86 (**10i**), 25.7 (**11i**), 22.51 (**10i**), 22.48 (**10i**), 22.45 (**11i**), 22.45 (**11i**), 20.47 (**11i**), 12.7 (**10i**).

***rac*-(3*R*,4*R*)-4-(2-((*Tert*-butyldimethylsilyl)oxy)ethyl)-3-methyloxetan-2-one (10j) and *rac*-(3*R*,4*R*)-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-4-methyloxetan-2-one (11j)**

General procedure H was followed using **1d** (13.2 mg, 0.0149 mmol, 7.49 mol %), THF (0.4 ml), and *tert*-butyldimethyl(2-((2*S*,3*R*)-3-methyloxiran-2-yl)ethoxy)silane (**9j**, 43.0 mg, 0.199 mmol). After stirring at 22 °C for 21 h, the crude reaction mixture was subjected to flash column chromatography to give a mixture of **10j** and **11j** (44.6 mg, 92%) as a colorless oil. Analytical data for **10j** has previously been reported in the literature.[66] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.52 (qd, *J* = 6.1, 4.0 Hz, 1H, **11j**), 4.32 (td, *J* = 6.6, 4.0 Hz, 1H, **10j**), 3.79–3.70 (m, 2H, **10j**), 3.71–3.65 (m, 2H, **11j**), 3.35 (qd, *J* = 7.6, 4.0 Hz, 1H, **10j**), 3.28 (ddd, *J* = 9.5, 5.4, 4.0 Hz, 1H,

11j), 2.07–1.91 (m, 2H + 2H, **10j** + **11j**), 1.55 (d, *J* = 6.1 Hz, 3H, **11j**), 1.39 (d, *J* = 7.6 Hz, 3H, **10j**), 0.88 (s, 9H + 9H, **10j** + **11j**), 0.05 (s, 6H + 6H, **10j** + **11j**). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.3 (**10j**), 171.5 (**11j**), 77.6 (**10j**), 75.5 (**11j**), 61.0 (**11j**), 59.1 (**10j**), 55.6 (**11j**), 51.1 (**10j**), 37.0 (**10j**), 30.9 (**11j**), 25.98 (**11j**), 25.97 (**10j**), 25.97 (**11j**), 20.3 (**11j**), 18.4 (**10j**), 12.5 (**10j**), -5.37 (**11j**), -5.38 (**10j**). **IR** (neat, cm^{-1}): 2955, 2857, 1823, 1472, 1253, 1095, 830, 775. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{25}O_3Si^+$ ($M + H^+$) 245.1567, found 245.1564.

***rac*-(3*R*,4*R*)-4-(3-((*Tert*-butyldimethylsilyl)oxy)propyl)-3-methyloxetan-2-one (10k) and *rac*-(3*R*,4*R*)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-4-methyloxetan-2-one (11k)**

General procedure H was followed using **1d** (8.9 mg, 0.0100 mmol, 5.00 mol %), THF (0.4 ml), and *tert*-butyldimethyl(3-((2*S*,3*R*)-3-methyloxiran-2-yl)propoxy)-silane[48] (**9k**, 46.0 mg, 0.200 mmol). After stirring at 22 °C for 21 h, the crude reaction mixture was subjected to flash column chromatography to give a mixture of **10k** and **11k** (44.9 mg, 87%) as a colorless oil. Analytical data for **10k** has previously been reported in the literature.[67] **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.40 (qd, *J* = 6.1, 3.9 Hz, 1H, **11k**), 4.22 (td, *J* = 6.8, 4.0 Hz 1H, **10k**), 3.68–3.61 (m, 2H + 2H, **10k** + **11k**), 3.25–3.18 (m, 1H + 1H, **10k** + **11k**), 1.93–1.78 (m, 2H + 2H, **10k** + **11k**), 1.70–1.53 (m, 2H + 2H, **10k** + **11k**), 1.54 (d, *J* = 6.1 Hz, 3H, **11k**), 1.38 (d, *J* = 7.6 Hz, 3H, **10k**), 0.88 (s, 9H + 9H, **10k** + **11k**), 0.04 (s, 6H + 6H, **10k** + **11k**). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.1 (**10k**), 171.3 (**11k**), 79.6 (**10k**), 74.8 (**11k**), 62.35 (**10k**), 62.34 (**11k**), 57.4 (**11k**), 50.9 (**10k**), 31.0 (**10k**), 29.9 (**11k**), 28.2 (**10k**), 26.03 (**11k**), 26.03 (**10k**),

24.5 (**11k**), 20.4 (**11k**), 18.42 (**10k**), 18.42(**11k**), 12.7 (**10k**), -5.23 (**10k**), -5.23(**11k**). **IR** (neat, cm^{-1}): 2929, 2857, 1823, 1472, 1254, 1094, 832, 774. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{27}O_3Si^+$ ($M + H^+$) 259.1724, found 259.1724.

2.5.2.8 Regioselective Carbonylation of cis-Epoxides Using Catalyst 7a

rac-(2_R_,3_R_)-Methyl 2-ethyl-3-hydroxybutanoate (12b)

General procedure I was followed using **7b** (14.3 mg, 0.0149 mmol, 5.02 mol %), $NaCo(CO)_4$ (3.3 mg, 0.017 mmol, 5.7 mol %), dioxane (0.3 ml), and *rac*-(2*S*,3*R*)-2-ethyl-3-methyloxirane[48] (**9b**, 0.990 M, dioxane, 300 µl, 0.297 mmol). After stirring at 22 °C for 21 h, the reactor was carefully vented in a well-ventilated hood. The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 20.0 mg, ca. 0.370 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **12b** (30.3 mg, 70%) as a colorless oil. The analytical data was in accordance with that reported in the literature.[68] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.91 (q, *J* = 5.5 Hz, 1H), 3.70 (d, *J* = 0.6 Hz, 3H), 2.55 (d, *J* = 5.5 Hz, 1H), 2.31 (dt, *J* = 8.7, 6.1 Hz, 1H), 1.73–1.59 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.0, 68.2, 54.4, 51.7, 22.7, 21.6, 11.8.

rac-(_R_)-Methyl 2-((_R_)-1-hydroxyethyl)pentanoate (12c)

General procedure I was followed using **7b** (14.4 mg, 0.0150 mmol, 5.07 mol %), dioxane (0.3 ml), $NaCo(CO)_4$ (3.0 mg, 0.015 mmol, 5.1 mol %) and *rac*-(2*R*,3*S*)-2-methyl-3-propyloxirane[48] (**9c**, 0.988 M, dioxane, 300 µl, 0.296 mmol). After stirring at

22 °C for 20 h, the reactor was carefully vented in a well-ventilated hood. The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 20.0 mg, ca. 0.370 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **12c** (36.4 mg, 77%) as a colorless oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.88 (h, *J* = 6.8 Hz, 1H), 3.69 (s, 3H), 2.57 (d, *J* = 7.1 Hz, 1H), 2.38 (dt, *J* = 9.3, 5.7 Hz, 1H), 1.70–1.45 (m, 2H), 1.29 (h, *J* = 7.3 Hz, 2H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.89 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.1, 68.5, 52.7, 51.7, 31.7, 21.7, 20.7, 14.1. **IR** (neat, cm^{-1}): 3452, 2958, 2874, 1735, 1435, 1169, 1117, 938. **HRMS** (ESI) *m/z* calculated for $C_8H_{16}NaO_3^+$ ($M + Na^+$) 183.0992, found 183.0998.

rac-(3_R_,4_R_)-4-Butyl-3-methyloxetan-2-one (12a) and _rac_-(3_R_,4_R_)-3-butyl-4-methyloxetan-2-one (11a)

General procedure I was followed using **7b** (14.4 mg, 0.0150 mmol, 5.00 mol %), dioxane (0.3 ml), $NaCo(CO)_4$ (3.0 mg, 0.015 mmol, 5.0 mol %) and *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane[49] (**9a**, 1.00 M, dioxane, 300 μl, 0.300 mmol). After stirring at 22 °C for 20 h, the reactor was carefully vented in a well-ventilated hood. The crude reaction mixture was subjected to bulb-to-bulb distillation to give a mixture of **12a** and **11a** (29.4 mg, 69%) as a yellow oil. Analytical data for **12a**[61] and **11a**[48] has previously been reported.

rac-(3_R_,4_R_)-3-Methyl-4-pentyloxetan-2-one (12d) and _rac_-(3_R_,4_R_)-4-methyl-3-pentyloxetan-2-one (11d)

General procedure I was followed using **7b** (14.4 mg, 0.0150 mmol, 5.00 mol %), dioxane (0.3 ml), $NaCo(CO)_4$ (3.0 mg, 0.015 mmol, 5.0 mol %) and *rac*-(2*R*,3*S*)-2-methyl-3-pentyloxirane[48] (**9d**, 1.00 M, dioxane, 300 µl, 0.300 mmol). After stirring at 22 °C for 20 h, the reactor was carefully vented in a well-ventilated hood. The crude reaction mixture was subjected to bulb-to-bulb distillation to give a mixture of **12d** and **11d** (34.7 mg, 74%) as a colorless oil. Analytical data for **12d**[64] and **11d**[48] has previously been reported. Only analytical data for **11d** is provided: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.39 (qd, *J* = 6.1, 4.0 Hz, 1H), 3.15 (ddd, *J* = 9.0, 6.5, 3.9 Hz, 1H), 1.86–1.66 (m, 2H), 1.55 (d, *J* = 6.1 Hz, 3H), 1.47–1.27 (m, 6H), 0.88 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.5, 74.8, 57.7, 31.5, 27.8, 26.7, 22.5, 20.5, 14.1.

rac-(3*R*,4*R*)-4-Hexyl-3-methyloxetan-2-one (12e) and _rac_-(3*R*,4*R*)-3-hexyl-4-methyloxetan-2-one (11e)

General procedure I was followed using **7b** (14.4 mg, 0.0150 mmol, 5.03 mol %), dioxane (0.3 ml), $NaCo(CO)_4$ (3.0 mg, 0.015 mmol, 5.0 mol %) and *rac*-(2*S*,3*R*)-2-hexyl-3-methyloxirane[48] (**9e**, 0.994 M, dioxane, 300 µl, 0.298 mmol). After stirring at 22 °C for 22 h, the reactor was carefully vented in a well-ventilated hood. The crude reaction mixture was subjected to bulb-to-bulb distillation to give a mixture of **12e** and **11e** (36.6 mg, 72%) as a colorless oil. Analytical data for **12e**[65] and **11e**[48] has previously been reported. Only analytical data for **11e** is provided: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.39 (qd, *J* = 6.1, 3.9 Hz, 1H), 3.15 (ddd, *J* = 8.8, 6.5, 3.9 Hz, 1H), 1.86–1.66 (m, 2H), 1.55 (d, *J* = 6.2 Hz, 3H), 1.46–1.23 (m, 8H), 0.87 (t, *J* = 6.7 Hz,

3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.5, 74.7, 57.7, 31.6, 29.0, 27.8, 26.9, 22.6, 20.4, 14.1.

***rac*-(2*R*,3*R*)-Methyl 3-hydroxy-2-phenethylbutanoate (12h)**

General procedure I was followed using **7b** (14.4 mg, 0.0150 mmol, 5.26 mol %), dioxane (0.3 ml), $NaCo(CO)_4$ (3.0 mg, 0.015 mmol, 5.3 mol %) and *rac*-(2*R*,3*S*)-2-methyl-3-phenethyloxirane (**9h**, 0.950 M, dioxane, 300 μl, 0.285 mmol). After stirring at 22 °C for 22 h, the reactor was carefully vented in a well-ventilated hood. The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 20.0 mg, ca. 0.370 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **12h** (52.6 mg, 83%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31–7.26 (m, 2H), 7.21–7.17 (m, 3H), 3.94 (p, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 2.70–2.55 (m, 3H), 2.45 (dddd, *J* = 9.4, 5.7, 4.8, 0.8 Hz, 1H), 2.09–1.99 (m, 1H), 1.90 (dddd, *J* = 14.0, 9.7, 6.9, 4.9 Hz, 1H), 1.22 (d, *J* = 7.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.7, 141.3, 128.50, 128.48, 126.1, 68.5, 52.3, 51.7, 33.6, 31.1, 21.6. **IR** (neat, cm^{-1}): 3440, 2951, 1717, 1454, 1198, 1160, 1029, 749, 699. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{18}NaO_3^+$ ($M + Na^+$) 245.1148, found 245.1155.

***rac*-(*R*)-Methyl 2-((*R*)-1-hydroxyethyl)-5-methylhexanoate (12i)**

General procedure I was followed using **7b** (14.4 mg, 0.0150 mmol, 5.00 mol %), dioxane (0.3 ml), $NaCo(CO)_4$ (3.0 mg, 0.015 mmol, 5.0 mol %) and *rac*-(2*S*,3*R*)-2-isopentyl-3-methyloxirane[48] (**9i**, 1.00 M, dioxane, 300 μl, 0.300 mmol). After stirring

at 22 °C for 20 h, the reactor was carefully vented in a well-ventilated hood. The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 20.0 mg, ca. 0.370 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **12i** (44.1 mg, 78%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.89 (p, *J* = 6.3 Hz, 1H), 3.69 (s, 3H), 2.54 (s, 1H), 2.33 (ddd, *J* = 9.3, 6.2, 5.2 Hz, 1H), 1.69–1.45 (m, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.22–1.04 (m, 2H), 0.86 (d, *J* = 3.1 Hz, 3H), 0.84 (d, *J* = 3.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.2, 68.5, 53.1, 51.7, 36.5, 28.2, 27.4, 22.7, 22.4, 21.7. **IR** (neat, cm^{-1}): 3453, 2954, 2871, 1736, 1435, 1168, 1116, 932. **HRMS** (ESI) *m/z* calculated for $C_{10}H_{20}NaO_3^+$ ($M + Na^+$) 211.1305, found 211.1317.

rac-(_R_)-Methyl 4-((_tert_-butyldimethylsilyl)oxy)-2-((_R_)-1-hydroxyethyl)butanoate (12j)

General procedure I was followed using **7b** (14.4 mg, 0.0150 mmol, 5.02 mol %), dioxane (0.3 ml), $NaCo(CO)_4$ (3.0 mg, 0.015 mmol, 5.0 mol %) and *rac-tert*-butyldimethyl(2-((2*S*,3*R*)-3-methyloxiran-2-yl)ethoxy)silane (**9j**, 0.998 M, dioxane, 300 μl, 0.299 mmol). After stirring at 22 °C for 20 h, the reactor was carefully vented in a well-ventilated hood. The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 20.0 mg, ca. 0.370 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **12j** (66.7 mg, 81%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.97–3.89 (m, 1H), 3.69 (s, 3H), 3.67 (dt, *J* = 11.6, 5.7 Hz, 1H), 3.58 (ddd, *J* = 10.4, 7.5, 5.2 Hz, 1H), 2.79 (d, *J* = 7.5 Hz, 1H), 2.60 (dt, *J* = 8.4, 5.4 Hz,

1H), 1.95–1.78 (m, 2H), 1.22 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 175.7, 68.3, 61.2, 51.7, 49.5, 32.1, 26.0, 21.5, 18.4, -5.4, -5.3. **IR** (neat, cm^{-1}): 3448, 2954, 2857, 1735, 1252, 1169, 1097, 832, 774. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{29}O_4Si^+$ ($M + H^+$) 277.1830, found 277.1837.

***rac*-(*R*)-Methyl 5-((*tert*-butyldimethylsilyl)oxy)-2-((*R*)-1-hydroxyethyl)pentanoate (12k)**

General procedure I was followed using **7b** (14.4 mg, 0.0150 mmol, 5.05 mol %), dioxane (0.3 ml), $NaCo(CO)_4$ (3.0 mg, 0.015 mmol, 5.1 mol %) and *rac-tert*-butyldimethyl(3-((2*S*,3*R*)-3-methyloxiran-2-yl)propoxy)silane[48] (**9k**, 0.991 M, dioxane, 300 µl, 0.297 mmol). After stirring at 22 °C for 21 h, the reactor was carefully vented in a well-ventilated hood. The crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 20.0 mg, ca. 0.370 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **12k** (69.7 mg, 80%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.92 (h, J = 6.4 Hz, 1H), 3.70 (s, 3H), 3.59 (t, J = 6.2 Hz, 2H), 2.49 (d, J = 6.9 Hz, 1H), 2.40 (dt, J = 8.0, 6.4 Hz, 1H), 1.71–1.64 (m, 2H), 1.52–1.46 (m, 2H), 1.22 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.1, 68.6, 62.7, 52.6, 51.7, 30.5, 26.1, 25.9, 21.7, 18.4, -5.2. **IR** (neat, cm^{-1}): 3460, 2953, 2857, 1737, 1254, 1096, 833, 774. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{31}O_4Si^+$ ($M + H^+$) 291.1986, found 291.2000.

***rac*-3-((2*R*,3*R*)-2-Methyl-4-oxooxetan-3-yl)propyl acetate (10l) and *rac*-3-((2*R*,3*R*)-3-methyl-4-oxooxetan-2-yl)propyl acetate (11l)**

General procedure I was followed using **7b** (14.4 mg, 0.0150 mmol, 5.00 mol %), dioxane (0.3 ml), $NaCo(CO)_4$ (3.0 mg, 0.015 mmol, 5.0 mol %) and *rac-cis*-1-acetoxy-4,5-epoxyhexane[51] (**9l**, 1.00 M, dioxane, 300 μl, 0.300 mmol). After stirring at 22 °C for 20 h, the reactor was carefully vented in a well-ventilated hood. The crude reaction mixture was concentrated under reduced pressure and then subjected to flash column chromatography to give a mixture of **10l** and **11l** (46.0 mg, 82%) as a colorless oil. Only analytical data for **11l** is provided: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.38 (qd, *J* = 6.1, 4.0 Hz, 1H), 4.05 (t, *J* = 6.1 Hz, 2H), 3.18 (td, *J* = 7.5, 4.0 Hz, 1H), 2.01 (s, 3H), 1.90–1.64 (m, 4H), 1.53 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.0, 170.8, 74.5, 63.5, 57.0, 26.0, 24.4, 21.0, 20.3. **IR** (neat, cm^{-1}): 2958, 1810, 1733, 1388, 1232, 1127, 1019, 825. **HRMS** (ESI) *m/z* calculated for $C_9H_{14}NaO_4^+$ ($M + Na^+$) 209.0784, found 209.0795.

2.5.2.9 Regioselective Chlorohydrin Formation From cis-Epoxides Using Catalyst 7b

rac-(2*R*,3*R*)-3-Chloroheptan-2-ol (14a)

General procedure J was followed using **7b** (14.8 mg, 0.0155 mmol, 5.20 mol %), THF (0.6 ml), 2,4,6-trimethylpyridine hydrochloride (52.3 mg, 0.332 mmol), and *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane[49] (**9a**, 34.0 mg, 0.298 mmol). The crude reaction mixture was subjected to bulb-to-bulb distillation to give **14a** (30.5 mg, 68%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.86–3.80 (m, 2H), 2.06 (d, J = 5.9 Hz, 1H), 1.84–1.71 (m, 2H), 1.58–1.49 (m, 1H), 1.45–1.25 (m, 3H), 1.28 (d, J = 6.0 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 70.7, 70.5, 34.5, 28.8, 22.4, 20.5, 14.1. **IR** (neat, cm^{-1}): 3389, 2957, 2931, 2862, 1457, 1378, 1144, 1050, 941, 835. **Elemental analysis:** $C_7H_{15}ClO$ (150.65), calculated C 55.81, H 10.04, Cl 23.53; found C 55.61, H 9.98, Cl 23.48. No molecular ion peak was observed when performing EI-MS or ESI-MS analysis, consequently no HRMS data was acquired.

rac-(2*R*,3*R*)-3-Chlorooctan-2-ol (14d)

General procedure J was followed using **7b** (14.4 mg, 0.0150 mmol, 4.93 mol %), THF (0.6 ml), 2,4,6-trimethylpyridine hydrochloride (52.0 mg, 0.330 mmol), and *rac*-(2*R*,3*S*)-2-methyl-3-pentyloxirane[48] (**9d**, 39.0 mg, 0.304 mmol). The crude reaction mixture was subjected to flash column chromatography to give **14d** (35.1 mg, 70%) as a colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.86–3.78 (m, 2H), 2.13 (d, J = 5.4 Hz, 1H), 1.83–1.69 (m, 2H), 1.61–1.50 (m, 1H), 1.47–1.22 (m, 5H), 1.27 (d, J = 6.0 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 70.7, 70.5, 34.7, 31.4,

26.4, 22.6, 20.4, 14.1. **IR** (neat, cm^{-1}): 3381, 2955, 2929, 2860, 1456, 1377, 1260, 1143, 1061, 961, 852. **Elemental analysis:** $C_8H_{17}ClO$ (164.67), calculated C 58.35, H 10.41, Cl 21.53; found C 57.43, H 9.99, Cl 21.42. No molecular ion peak was observed when performing EI-MS or ESI-MS analysis, consequently no HRMS data was acquired.

***rac*-(2*R*,3*R*)-3-Chlorononan-2-ol (14e)**

General procedure J was followed using **7b** (14.3 mg, 0.0149 mmol, 5.03 mol %), THF (0.6 ml), 2,4,6-trimethylpyridine hydrochloride (52.0 mg, 0.330 mmol), and *rac*-(2*S*,3*R*)-2-hexyl-3-methyloxirane[48] (**9e**, 42.3 mg, 0.297 mmol). The crude reaction mixture was subjected to flash column chromatography to give **14e** (40.8 mg, 77%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.85–3.79 (m, 2H), 2.09 (d, J = 5.7 Hz, 1H), 1.83–1.70 (m, 2H), 1.59–1.51 (m, 1H), 1.46–1.23 (m, 7H), 1.27 (d, J = 5.8 Hz, 3H), 0.90–0.87 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 70.7, 70.5, 34.7, 31.8, 28.9, 26.7, 22.7, 20.5, 14.2. **IR** (neat, cm^{-1}): 3384, 2925, 2857, 1457, 1377, 1259, 1142, 838. **Elemental analysis:** $C_9H_{19}ClO$ (178.70), calculated C 60.49, H 10.72, Cl 19.84; found C 60.32, H 10.66, Cl 19.74. No molecular ion peak was observed when performing EI-MS or ESI-MS analysis, consequently no HRMS data was acquired.

***rac*-(2*R*,3*R*)-3-Chloro-4-phenylbutan-2-ol (14g)**

General procedure J was followed using **7b** (21.5 mg, 0.0225 mmol, 7.50 mol %), THF (0.6 ml), 2,4,6-trimethylpyridine hydrochloride (52.0 mg, 0.330 mmol), and *rac*-(2*S*,3*R*)-2-benzyl-3-methyloxirane (**9g**, 44.5 mg, 0.300 mmol). The crude reaction

mixture was subjected to flash column chromatography to give **14g** (30.7 mg, 55%) as a colorless oil. The analytical data was in accordance with that reported in the literature.[69] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.35–7.31 (m, 2H), 7.28–7.25 (m, 3H), 4.05 (ddd, *J* = 8.2, 6.5, 3.2 Hz, 1H), 3.91–3.84 (m, 1H), 3.23 (dd, *J* = 14.0, 6.5 Hz, 1H), 3.07 (dd, *J* = 14.0, 8.1 Hz, 1H), 1.97 (d, *J* = 8.1 Hz, 1H), 1.32 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 137.8, 129.5, 128.7, 127.0, 70.1, 68.6, 41.3, 21.1.

***rac*-(2*R*,3*R*)-3-Chloro-5-phenylpentan-2-ol (14h)**

General procedure J was followed using **7b** (14.4 mg, 0.0150 mmol, 4.95 mol %), THF (0.6 ml), 2,4,6-trimethylpyridine hydrochloride (52.0 mg, 0.330 mmol), and *rac*-(2*R*,3*S*)-2-methyl-3-phenethyloxirane (**9h**, 49.2 mg, 0.303 mmol). The crude reaction mixture was subjected to flash column chromatography to give **14h** (45.1 mg, 75%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.33–7.30 (m, 2H), 7.23–7.21 (m, 3H), 3.88–3.82 (m, 1H), 3.79 (ddd, *J* = 7.9, 6.1, 4.5 Hz, 1H), 2.94 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.77 (dt, *J* = 13.9, 8.2 Hz, 1H), 2.13–2.08 (m, 3H), 1.27 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 140.9, 128.64, 128.64, 126.3, 70.6, 69.3, 36.3, 32.8, 20.4. **IR** (neat, cm^{-1}): 3390, 2931, 1454, 1375, 1126, 1029, 909, 749, 699. **Elemental analysis:** $C_{11}H_{15}ClO$ (198.69), calculated C 66.49, H 7.61, Cl 17.84; found C 66.49, H 7.67, Cl 17.92. No molecular ion peak was observed when performing EI-MS or ESI-MS analysis, consequently no HRMS data was acquired.

***rac*-(2*R*,3*R*)-3-Chloro-6-methylheptan-2-ol (14i)**

General procedure J was followed using **7b** (14.3 mg, 0.0149 mmol, 5.03 mol %), THF (0.6 ml), 2,4,6-trimethylpyridine hydrochloride (52.0 mg, 0.330 mmol), and *rac*-(2*S*,3*R*)-2-isopentyl-3-methyloxirane[48] (**9i**, 38.0 mg, 0.296 mmol). The crude reaction mixture was subjected to flash column chromatography to give **14i** (33.1 mg, 68%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.87–3.79 (m, 2H), 2.05 (d, *J* = 6.2 Hz, 1H), 1.86–1.70 (m, 2H), 1.62–1.51 (m, 1H), 1.44 (dddd, *J* = 13.1, 10.7, 7.2, 4.7 Hz, 1H), 1.35–1.25 (m, 1H), 1.28 (d, *J* = 6.1 Hz, 3H), 0.90 (t, *J* = 6.6 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 71.1, 70.5, 35.8, 32.7, 27.9, 22.9, 22.4, 20.5. **IR** (neat, cm^{-1}): 3391, 2955, 1468, 1367, 1253, 1147, 1110, 1025, 967, 777. **Elemental analysis:** $C_8H_{17}ClO$ (164.67), calculated C 58.35, H 10.41, Cl 21.53; found C 58.49, H 10.50, Cl 21.62. No molecular ion peak was observed when performing EI-MS or ESI-MS analysis, consequently no HRMS data was acquired.

2.5.2.10 Low Quality Crystal Data for Catalyst 1m

To date, only low quality crystals of catalyst **1m** could be obtained due to the pronounced propensity of **1m** for crystal twinning when crystallized from a solution in THF that had been layered with a hydrocarbon solvent such as heptane. Use of other ethereal (Et_2O, THP, DME) or hydrocarbon (pentane, hexanes, cyclohexane) solvents gave no / unsuitable crystals.

Table 2.13 Selected parameters of the low quality crystal data for catalyst 1m

Empirical formula	$C_{58}H_{72}AlCoN_2O_8$	
Formula weight	1011.09	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 15.8411(8) Å	α = 90°
	b = 53.450(3) Å	β = 94.792(3)°
	c = 16.2954(8) Å	γ = 90°
Volume	13749.1(12) $Å^3$	
Z	8	
Final R indices [I>2sigma(I)]	R1 = 0.0707, wR2 = 0.1832	
R indices (all data)	R1 = 0.1038, wR2 = 0.2010	

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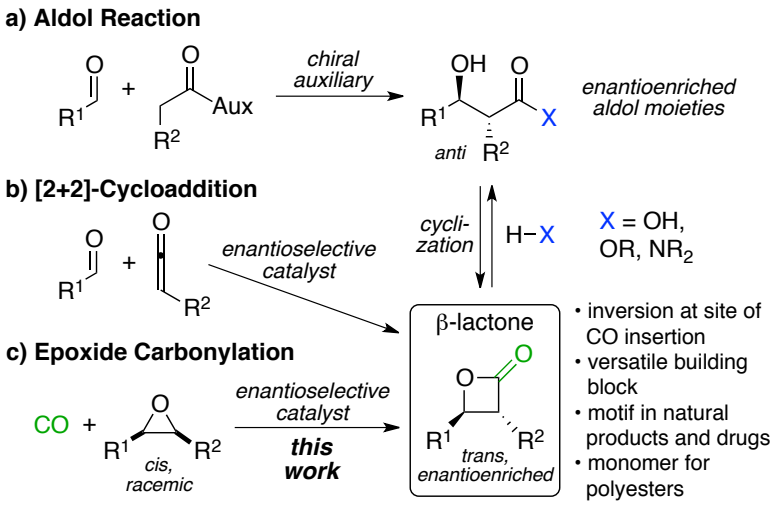
CHAPTER THREE

Development of New Catalyst Frameworks for the Synthesis of Enantioenriched β-Lactones from *Racemic* or *Meso cis*-Disubstituted Epoxides

3.1 Introduction

β-Lactones have a long-standing history as valuable and versatile compounds in chemical synthesis. Their usage includes areas such as the synthesis of natural products,[1] pharmaceutical compounds,[2] (biodegradable) polyesters,[3] the labeling of proteins,[4] and the use as precursors to value-added products with structural complexity.[5] Moreover, the high intrinsic reactivity of the strained β-lactone ring allows reaction with a variety of nucleophiles to form products typically associated with aldol chemistry (Scheme 3.1).[6,7] The resulting aldol moieties are also important motifs in natural products.[8]



Scheme 3.1 Common approaches to enantioenriched β-lactones, with epoxide carbonylation as an attractive alternative

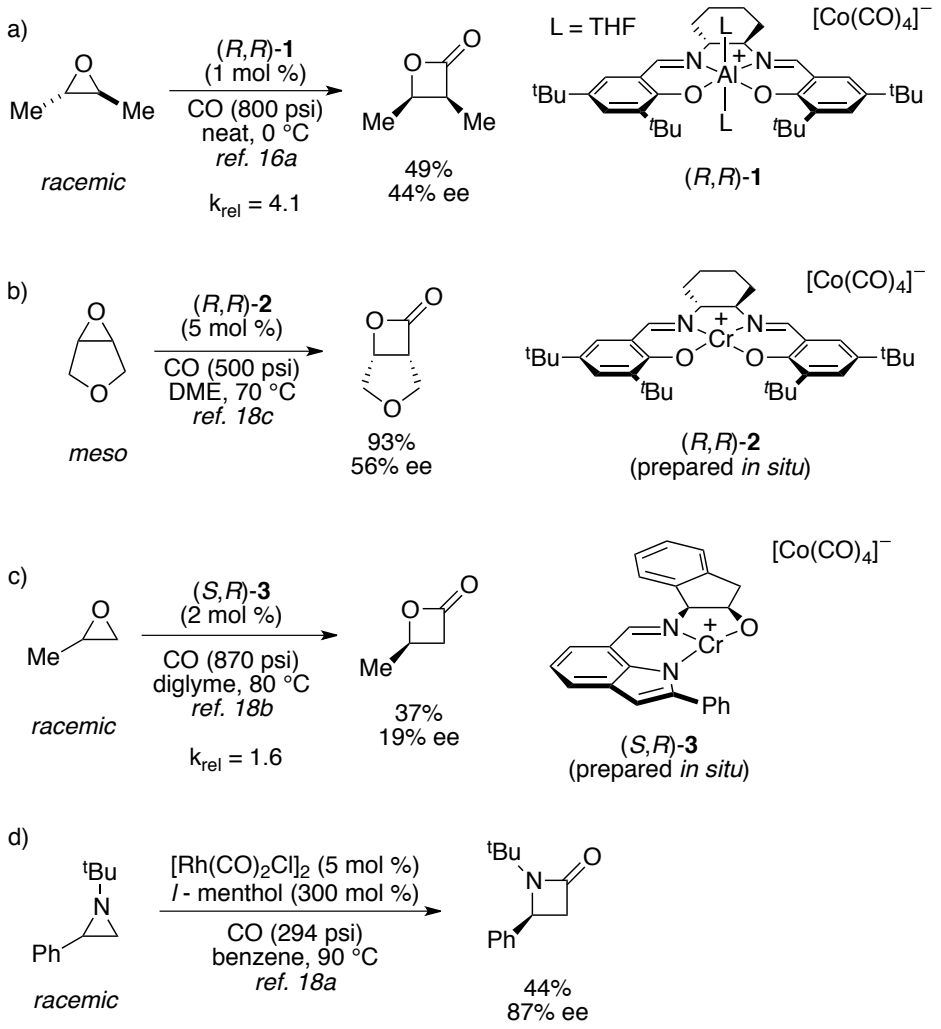
Although a variety of synthetic methodologies are available to access β-lactone products, methods for the direct, economical and enantioselective synthesis of β-lactones are still limited,[9] thus restricting their utility. In the past, aldol chemistry has often been used to access (enantioenriched) β-lactones (Scheme 3.1a).[6] Many highly

diastereo- and enantioselective aldol reactions furnish suitable intermediates[10] that can then be cyclized to the desired β-lactone.[6] However, most aldol methodologies suffer from the requirements of preformed enolate-equivalents together with enantiopure auxiliaries or catalysts. Consequently, this route to β-lactones can be impractical and costly, although recent developments in the field of asymmetric direct aldol reactions may alleviate these concerns.[11]

A more recent approach yielding enantioenriched β-lactones directly is based on (formal) [2+2]-cycloadditions of aldehydes with ketenes (Scheme 3.1b).[12] These reactions routinely give *cis*-configured β-lactones with high stereoselectivity, but only a few catalytic systems for the synthesis of enantioenriched *trans*-β-lactones are reported.[13,14] For example, Calter and coworkers described an organocatalytic approach showing excellent enantioselectivities, yet high catalyst loadings were needed and the scope was limited.[13a] Peters and coworkers disclosed a very elegant aluminum-catalyzed method yielding a broad variety of *trans*-β-lactones in good enantiomeric excess and yields.[13b-d] However, high catalyst loadings, low temperatures, and preparation of the catalyst with pyrophoric reagents just prior to use were required. In addition, diminished enantiomeric ratios for the important class of α-methyl-substituted β-lactones were observed.

Another direct approach to β-lactones is the carbonylation of epoxides using catalysts of the form $[\text{Lewis acid}]^+[Co(CO)_4]^-$ (Scheme 3.1c).[15] This method is attractive because carbon monoxide and diastereopure epoxides are readily available. Furthermore, the reaction is proposed to follow by an S_N2-mechanism,[16] which reliably transforms stereochemistry already present in the epoxide. For example, *cis*-

epoxides are cleanly converted into *trans*-β-lactones as shown in Scheme 3.1c. However, enantioselective variants of these reactions such as carbonylative kinetic resolution or *meso* desymmetrization of epoxides still have not reached synthetically useful levels, and were declared a major challenge for the field.[17] Scheme 3.2 summarizes the precedence from the literature.[16a,18]



Scheme 3.2 Examples of previously reported catalytic systems for the asymmetric carbonylation of epoxides and aziridines

One of the best examples so far was reported by Ibrahim and coworkers (Scheme 3.2b). Using catalyst (*R*,*R*)-**2**, they achieved moderate ee's in the range of 11-56% in the carbonylative desymmetrization of a number of alicyclic *meso* epoxides.[18c]

In an effort to advance the field of asymmetric epoxide carbonylation, we herein report two new enantiopure carbonylation catalysts. Both catalysts are active for 1) the carbonylative desymmetrization of aliphatic *meso* epoxides, and 2) the regiodivergent carbonylation of *racemic cis*-disubstituted epoxides. In both cases, the resulting α,β-disubstituted β-lactones show high enantiomeric excess and *trans*-configuration, which makes these methods complementary to the advances in the field of [2+2]-cycloadditions. Furthermore, the enantioenriched β-lactones can easily be converted into *anti*-aldol products. This transformation is important because aldol reactions giving rise to *anti*-β-hydroxycarbonyl moieties[19] are less developed than those giving *syn*-aldol products.[20] Consequently, enantioenriched *anti*-aldol products are less readily available than their *syn*-counterparts by either aldol reactions or [2+2]-cyclo-additions, thus further underscoring the importance of this study.

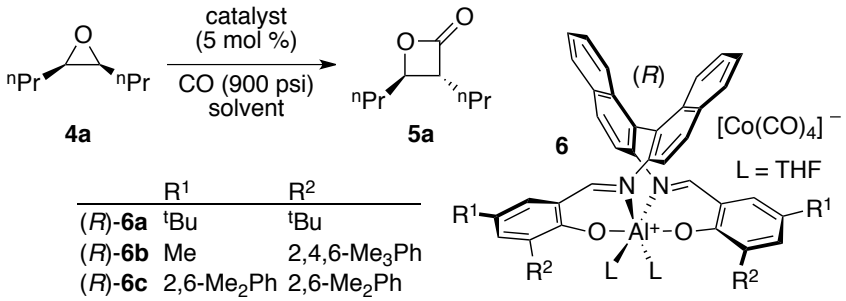
3.2 Desymmetrization of Meso Epoxides

3.2.1 Catalyst Development

Initial efforts focused on the carbonylative desymmetrization of *meso* epoxides because only one product can arise from such epoxides in contrast to *racemic cis*- or *trans*-disubstituted epoxides (*vide infra*, Scheme 3). The precedence shown in Scheme 3.2 guided the search for a suitable catalytic system. Salen-based ligands seemed an ideal platform for ligand development. Their highly modular nature and demonstrated ability to induce higher levels of enantioselectivity in comparison to porphyrin-ligands[18c] made them very attractive.

As a starting point, previously reported catalysts (*S*,*S*)-**1** and (*R*,*R*)-**2** were tested for the carbonylative desymmetrization of *meso* epoxide **4a** (Table 3.1, entries 1 and 2). Both catalysts gave unsatisfactory levels of enantioselectivity and activity. Interestingly, the aluminum-based system **1** performed slightly better than its chromium-analog **2**, which made aluminum the metal of choice for future Lewis acids. In light of these results, we speculated that the flat geometry of the ligand framework in **1** and **2** was the main reason for the modest degree of enantioenrichment observed in lactone **5a**. Salen-catalysts that bear aryl-moieties as substituents R^2, on the other hand, deviate from this planarity, and the success of such catalysts in the regioselective carbonylation of *trans*-disubstituted epoxides[21] made them promising candidates. Unfortunately, the results obtained with this class of catalysts were still not satisfactory in terms of activity and selectivity. Further inspiration for improvement

Table 3.1 Evaluation of enantiopure [Lewis acid]$^+$ [Co(CO)$_4$]$^-$-catalysts and reaction parameters for the carbonylative desymmetrization of *meso* epoxides[a]



	R^1	R^2
(*R*)-**6a**	^{t}Bu	^{t}Bu
(*R*)-**6b**	Me	2,4,6-Me$_3$Ph
(*R*)-**6c**	2,6-Me$_2$Ph	2,6-Me$_2$Ph

entry	catalyst[b]	solvent	β-lactone **5a**[c]	
			conv. (%)	conv. (%)
1	(*S*,*S*)-**1**	THF	43	16
2	(*R*,*R*)-**2**	THF	5	-12
3	(*R*)-**6a**	THF	89	58
4	(*R*)-**6b**	THF	70	94
5	(*R*)-**6c**	THF	42	97
6	(*R*)-**6b**	THP	78	73
7	(*R*)-**6b**	1,4-dioxane	98	70
8	(*R*)-**6b**	DME	7	24
9	(*R*)-**6b**	toluene	98	43
10[d]	(*R*)-**6b**	THF	68	94
11[e]	(*R*)-**6b**	THF	65	94
12[f]	(*R*)-**6b**	THF	>95	87

[a]Reaction conditions: [**4a**] = 0.5 M, 22 °C, 12 h. [b]Catalyst generated *in situ* (L_nAlCl + $NaCo(CO)_4$), except for entry 1. [c]Conversion to β-lactone and enantiomeric excess determined by GC analysis. [d]450 psi CO used. [e]5 mol % $NaCo(CO)_4$ added. [f]Run at 40 °C.

came from work in our group that used salen-catalysts based on 1,1'-binaphthyl-2,2'-diamine (DABN).[22] The DABN-unit twists the salen-ligand, thus decreasing its planarity. Moreover, DABN-based catalysts have been used successfully in other asymmetric transformations, and also make other coordination geometries such as *cis*-

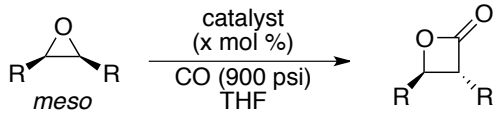
α or *cis*-β more accessible.[23] Indeed, use of DABN in the form of (*R*)-**6a** gave good initial results (entry 3). Combining the DABN-unit contained in (*R*)-**6a** with salicylaldehydes bearing aryl-moieties as substituents R^2 then yielded catalyst (*R*)-**6b**, which finally showed good activity and excellent enantioselectivity (entry 4). Increasing the steric hindrance around the Lewis acid improved selectivity even further (catalyst (*R*)-**6c**, entry 5), but at the same time decreased activity. Attempts to improve the activity of (*R*)-**6b** by using solvents other than THF were successful yet the degree of enantiomeric excess suffered greatly (entries 6-9). Variation of CO pressure, reaction temperature, or addition of excess $Na[CO(CO)_4]$ showed no further benefit (entries 10-13). Lastly, it should be noted that catalysts (*R*)-**6a-c** were generated *in situ* for all experiments by mixing the corresponding aluminum chloride precursor with $Na[CO(CO)_4]$ just prior to the reaction. This approach was taken because (*R*)-**6b** and **c** upon isolation showed a degree of solvation that was hard to quantify, and consequently made weighing out defined amounts of catalyst difficult. *In situ* generation of carbonylation catalysts has also been used successfully by others.[24]

3.2.2 Scope of the Carbonylative Desymmetrization of Meso Epoxides

With competent catalytic systems in hand, the scope of the carbonylative desymmetrization of *meso* epoxides **4** was explored (Table 3.2). So far, only aliphatic *meso* epoxides have been found to be active with catalysts (*R*)-**6b** and (*R*)-**6c** at 22 °C. This is remarkable because the majority of reported desymmetrization reactions for *meso* epoxides are geared towards alicyclic *meso* epoxides.[25] Of the *meso* epoxides tested with (*R*)-**6b**, all showed yields greater than 70% and good to excellent levels of

enantioenrichment. Moreover, an inverse correlation between the steric size of the substrate and the activity of (*R*)-**6b** was noted, with bulkier epoxides requiring higher catalyst loadings and slightly elevated reaction temperatures (cf. entries 1 and 5). Interestingly, increasing the steric size of the epoxide also led to larger amounts of ketone side-products, which stem from rearrangement reactions of the epoxide.[16b] In addition, a trend in terms of enantioselectivity manifested itself, with epoxides such as **4a** and **c** giving the best results (entries 2 and 3).

Table 3.2 Scope of the carbonylative desymmetrization of *meso* epoxides 4 using catalysts (*R*)-6b and (*R*)-6c[a]



meso **4a-e** **5a-e**

entry	R	catalyst	mol % catalyst	isol. product	isol. yield (%)	%ee[b]
1	Me	(*R*)-**6b**	2.5	**5b**	95[c]	83
2	Et	(*R*)-**6b**	4	**5c**	70	95
3	^{n}Pr	(*R*)-**6b**	7	**5a**	77	94
4	^{n}Bu	(*R*)-**6b**	8	**5d**	72	92
5[d]	$(CH_2)_3OCH_2CF_3$	(*R*)-**6b**	12.5	**5e**	79	84
6	Me	(*R*)-**6c**	2.5	**5b**	94[c]	83
7	Et	(*R*)-**6c**	6	**5c**	74	98
8	^{n}Pr	(*R*)-**6c**	10	**5a**	76	97
9	^{n}Bu	(*R*)-**6c**	12	**5d**	72	91

[a]Reaction conditions: [**4**] = 0.5 M, 22 °C, 24 h. All reactions gave full conversion by GC analysis. [b]Enantiomeric excess determined by GC analysis. [c]Yield determined by GC analysis using method of standard addition. [d]Run at 33 °C. Catalysts (*R*)-**6b** and (*R*)-**6c** were generated *in situ* (L_nAlCl + $NaCo(CO)_4$).

Use of the bulkier catalyst (*R*)-**6c** gave results and trends similar to those seen with (*R*)-**6b**. In the case of epoxide **4b**, the same enantiomeric excess was observed with either catalyst (entries 1 and 6). This substrate is apparently too small to be affected by the additional steric bulk of (*R*)-**6c**. In other cases, improved enantiomeric excess of the β-lactone product was obtained, which however occurred at the expense of higher catalyst loadings (entries 7 and 8). All in all, catalysts (*R*)-**6b** and (*R*)-**6c** were well suited for the carbonylative desymmetrization of aliphatic *meso* epoxides, which nicely complements analogous work on alicyclic *meso* epoxides carried out by Ibrahim and coworkers.[18c]

3.2.3 Solid State Structure of Catalyst (R)-6b

Single crystals of (*R*)-**6b** were obtained and subjected to X-ray analysis to further understand the mode of action of this catalyst (Figure 3.1).

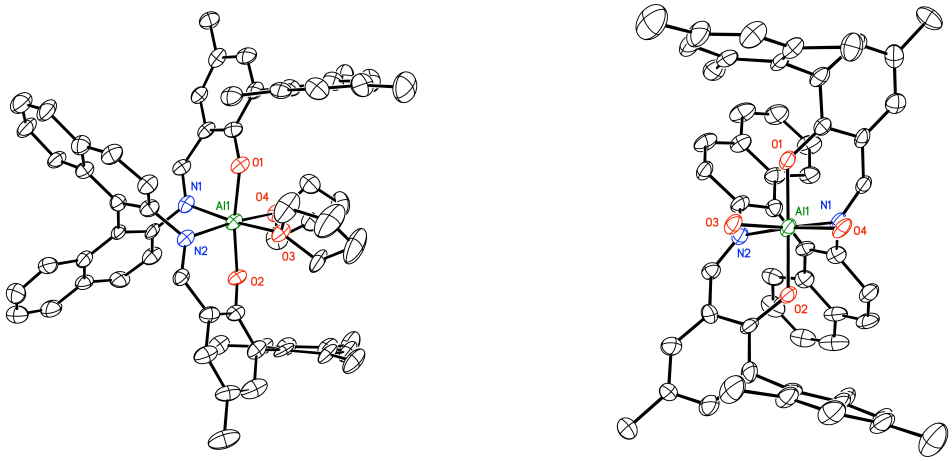


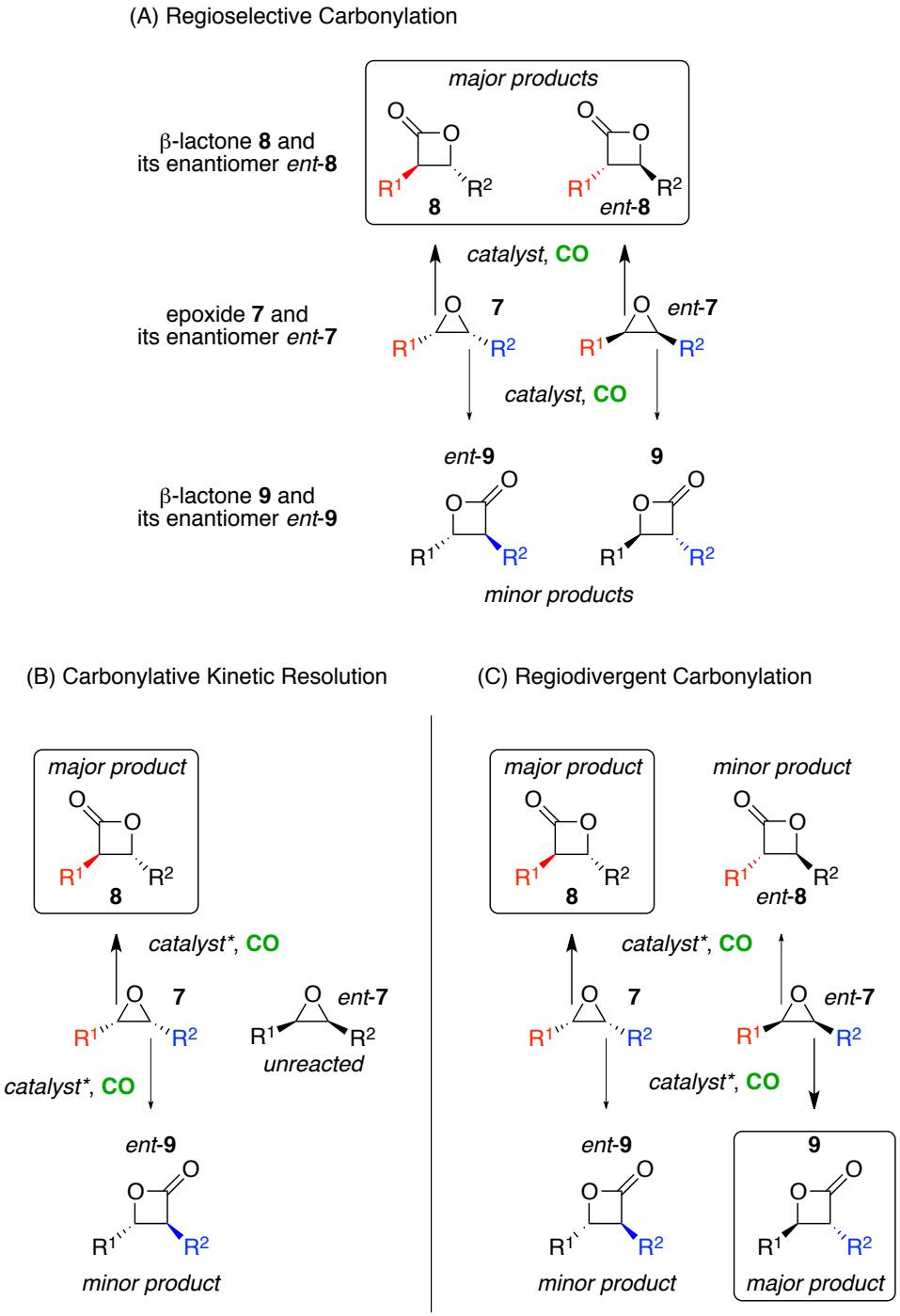
Figure 3.1 ORTEP-representations of catalyst (*R*)-6b with thermal ellipsoids drawn at 40% probability. Hydrogen atoms, cobaltate counterion and solvent molecules omitted / truncated for clarity.

The solid state structure shows the expected ion pair composed of [Lewis acid]$^+$ and $[Co(CO)_4]^-$. More interestingly, the ligand around the aluminum-ion adopts *cis*-α geometry, which is a departure from the *trans*-planar structures of previously reported salen-based carbonylation catalysts.[15] The strong twist imposed by the DABN-unit in combination with the steric interaction of the mesityl-groups are most likely the main causes for this arrangement of the ligand. In support of this, an analog of (*R*)-**6a** shows *cis*-β geometry,[26] whereas use of a more flexible diamine-unit gives a *trans*-planar coordinated salen-complex.[27] Nonetheless, this *cis*-α geometry allows for formation of a rigid and C_2-symmetric chiral pocket occupied by two THF-molecules. This structure also explains why DME was a particularly poor solvent for (*R*)-**6b** (Table 3.1, entry 8). DME can act as a bidentate ligand, thus occupying both *cis*-coordination sites. Due to the chelate effect, it would then be able to compete with epoxide molecules for binding to the Lewis acid.

3.3 Regiodivergent Carbonylation of Racemic cis-Disubstituted Epoxides

3.3.1 Background

Given the strong performance of (*R*)-**6b** and (*R*)-**6c** in the carbonylation of *meso* epoxides, a logical extension was to investigate the carbonylation of *racemic cis*-disubstituted epoxides. However, achieving synthetically useful asymmetric reactions with this class of epoxides is much more challenging. A nucleophile reacting with such epoxides has to differentiate not only between the two different epoxide enantiomers, but also between the two different epoxy-methine-carbons within each enantiomer. Consequently, even reacting such epoxides with achiral catalysts and reagents can be difficult, resulting in a mixture of two regioisomeric products. As was mentioned in Chapter 1, potential solutions to this problem include 1) installation of a strong steric/electronic bias in the epoxide, or 2) use of a catalyst that promotes formation of only one of the two regioisomers. The second approach is undoubtedly more elegant, but catalytic systems that give high levels of regioselectivity in S_N2-reactions of unbiased *racemic cis*- or *trans*-disubstituted epoxides are exceedingly rare (cf. Chapter 2). The general idea behind the regioselective reaction of a *racemic* epoxide is shown in Scheme 3.3A. Each enantiomer of the carbonylation catalyst reacts preferentially with only one enantiomer of the epoxide, and selectively inserts CO next to epoxide-substituent R^1. The result is a *racemic* mixture of only one of the two possible β-lactone regioisomers.



Scheme 3.3 Range of possible β-lactone products from the carbonylation of *racemic cis*-disubstituted epoxides. Use of a regioselective carbonylation catalyst that is *racemic* or *achiral* results in *Regioselective Carbonylation* (A). If the same catalyst is enantiopure and only consumes **7**, *Carbonylative Kinetic Resolution* (B) ensues. A regioselective, enantiopure catalyst that consumes both **7** and *ent*-**7** with opposing regioselectivities gives *Regiodivergent Carbonylation* (C). *Catalyst** denotes an enantiopure carbonylation catalyst. CO = carbon monoxide.

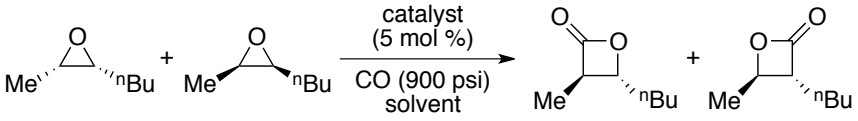
If an enantiopure version of the same catalyst is employed, and if it converts one enantiomer of the epoxide much faster than the other, one obtains a classical kinetic resolution (Scheme 3.3B).[28,30c] The resulting product would now be an enantio-enriched β-lactone, and if the regioselectivity of the catalyst is still high, one obtains only one of the two possible enantioenriched regioisomers. In practice, however, both enantiomers of the epoxide tend to react with comparable rates, and one still obtains a mixture of regioisomers and only modest enantiomeric enrichment. As a result, efficient kinetic resolutions of *racemic cis*- or *trans*-disubstituted epoxides have largely remained elusive.[29]

A possible third scenario, shown in Scheme 3.3C, belongs to the recently burgeoning field of (regio-)divergent reactions.[30] Here, both enantiomers of the epoxide react with an enantiopure catalyst, but the catalyst displays opposing regioselectivities for each epoxide enantiomer. The outcome of such a reaction would be the formation of two regioisomeric β-lactones that both are highly enantioenriched. Consequently, the requirements of a successful catalyst would be that its regiopreference must be stronger than any steric or electronic bias contained in substituents R^1 and R^2 of the epoxide. Furthermore, the catalyst must still be able to distinguish between the two epoxide enantiomers. Unsurprisingly, few regiodivergent reactions based on an S_N2-reaction have been reported so far outside the realm of enzyme-catalysis, especially with epoxides as substrates.[31]

3.3.2 Catalyst Evaluation

When testing catalyst (*R*)-**6b** with *racemic cis*-disubstituted epoxide **7a**, the formation of two regioisomeric *trans*-β-lactones **8a** and **9a** was observed, the enantiomeric excess of which were excellent and good respectively (Table 3.3, entry 1). A kinetic resolution could not account for this observation, whereas invoking the occurrence of a regiodivergent reaction[30] could (Scheme 3.3C).

Table 3.3 Evaluation of enantiopure [Lewis acid]$^+$[Co(CO)$_4$]$^-$-catalysts and solvents for the regiodivergent carbonylation of *cis*-epoxides[a]



7a *ent*-**7a** **8a** **9a**

entry	catalyst	solvent	lactone **8a**[b]		lactone **9a**[b]	
			conv. (%),	%ee	conv. (%),	%ee
1	(*R*)-**6b**	THF	43	94	53	83
2	(*R*)-**6b**	toluene	44	86	54	73
3	(*R*)-**6b**	Et_2O	46	87	53	77
4	(*R*)-**6b**	DME	11	58	17	79
5	(*R*)-**6b**	THP	43	87	54	72
6	(*R*)-**6b**	1,4-dioxane	44	85	55	72
7	(*R*)-**6c**	THF	49	90	51	91
8	(*R*,*R*)-**1**	THF	72	<1	26	8
9	(*R*)-**6a**	THF	61	30	33	49

[a]Reaction conditions: [epoxide] = 0.5 M, 22 °C, 16 h. [b]Conversion to respective β-lactone and enantiomeric excess determined by GC analysis. Catalysts (*R*)-**6a**-**c** were generated *in situ* (L_nAlCl + $NaCo(CO)_4$).

Regiodivergent carbonylation of methyl-*cis*-disubstituted epoxides such as **7a** are especially attractive because the resulting *trans*-β-lactones **8** and **9** are both potentially

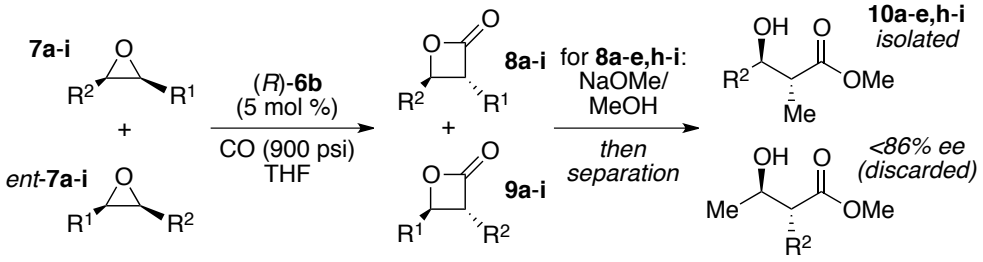
useful. Lactone **8** can be transformed into enantioenriched propionate aldol units with *anti*-configuration. Such compounds are often used in the synthesis of natural products.[8c] β-Lactone **9**, on the other hand, represents aldol products based on acetaldehyde, which is a troublesome electrophile for aldol reactions because of its suspected carcinogenicity and propensity to hydrate or oligomerize.

Given the good initial results with catalyst (*R*)-**6b**, further attempts were made to increase the enantiomeric excess for **9a** by using different solvents. None of the solvents tested surpassed the results obtained with THF (entries 2-6). However, it was found that (*R*)-**6c** yielded both β-lactones with very good enantiomeric excess (entry 7). (*R*)-**6b** and (*R*)-**6c** are nonetheless complementary, with (*R*)-**6b** showing the best enantiomeric excess for **8a**, whereas (*R*)-**6c** gave slightly lower but still excellent values for both **8a** and **9a**. As expected, previously reported catalysts such as (*R*,*R*)-**1** or (*R*)-**6a** failed to reach similar levels of selectivity (entries 8 and 9).

3.3.3 Scope of the Regiodivergent Carbonylation of Racemic cis-Epoxides

Encouraged by the screening results, the scope of this reaction using a variety of *racemic cis*-disubstituted epoxides **7** and catalyst (*R*)-**6b** was investigated next (Table 3.4). The resulting lactones **8** and **9** all showed high levels of enantioenrichment, but none of them could be separated quantitatively using flash column chromatography.

Table 3.4 Scope of the regiodivergent carbonylation of *racemic cis*-epoxides using catalyst (*R*)-6b[a]



entry	R^1	R^2	isol. product	isol. yield (%)	%ee[b]
1	Me	Et	**10b**	38	94
2	Me	^{n}Pr	**10c**	32	93
3	Me	^{n}Bu	**10a**	36	94
4	Me	^{n}Pent	**10d**	36	94
5	Me	^{n}Hex	**10e**	33	95
6	Et	^{n}Pr	**8f** + **9f**	61[c]	96 (**8f**), 93 (**9f**)
7	Et	^{n}Bu	**8g** + **9g**	73[c]	96 (**8g**), 90 (**9g**)
8	Me	$(CH_2)_2{}^i$Pr	**10h**	36	94
9	Me	$(CH_2)_3$OTBS	**10i**	35	92

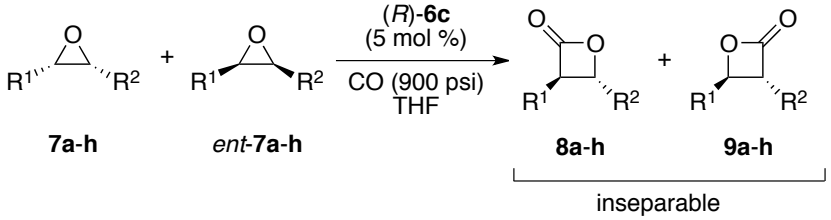
[a]Reaction conditions: [*rac*-**7**] = 0.5 M, 22 °C, 20 h. All reactions gave full conversion by GC analysis. [b]Enantiomeric excess determined by GC analysis. [c]Isolated yield of combined β-lactones **8** and **9**. TBS = ^{t}BuMe$_2$Si. Catalyst (*R*)-**6b** was generated *in situ* (L_nAlCl + NaCo(CO)$_4$).

However, this inseparability is of little concern if one is interested in the resulting aldol-type products, because ring-opening of lactones **8a-e,h-i** and **9a-e,h-i** to the corresponding methyl-esters enabled facile separation of the two species. Using this approach, lactones **8a-e,h-i** were converted into methyl-esters **10a-e,h-i** *via* a one-pot procedure, and isolated as such. Lactones **9a-e,h-i** (with R^1 = Me) generally showed less than 86% ee, which did not warrant isolation of their ester-derivatives.

Good yields and excellent enantioselectivities of 93% ee or better were achieved for methyl-esters **10a-e** bearing linear alkyl-chains of varying length as R^2 (entries 1-5). Epoxides with branching in R^2 performed equally well and produced esters **10h-i** with comparable yields and enantioenrichment (entries 8 and 9). Ethyl-substituted epoxides **7f** and **7g** also gave good enantiomeric excess for **8** and **9** (entries 6 and 7), but even their ester-derivatives were difficult to separate. Therefore, a mixture of the two lactones was isolated in both cases. Overall, (*R*)-**6b** proved to be an excellent catalyst for the production of highly enantioenriched lactones **8** and the corresponding esters **10** from *racemic* epoxides **7**. Consequently, (*R*)-**6b** is the catalyst of choice if highly enantioenriched propionate aldol-type products are desired.

Given the good performance of (*R*)-**6c** in the carbonylative *meso* desymmetrization reaction (Table 3.2, entries 6-9) and in the screen with *cis*-disubstituted epoxides (Table 3.3, entry 7), its behavior in the regiodivergent carbonylation of *racemic cis*-epoxides was also investigated. Consequently, a variety of *racemic cis*-epoxides **7** were carbonylated using (*R*)-**6c** (Table 3.5) using the same conditions as before in Table 3.4. In all cases, the formation of two regioisomeric *trans*-β-lactones **8** and **9** in a ratio of approximately 1 : 1 was observed. More

Table 3.5 Scope of the regiodivergent carbonylation of *cis*-epoxides using catalyst (*R*)-6c[a]



entry	R^1	R^2	isol. product	isol. yield (%)	ratio[b] **8** : **9**	%ee[c]
1[d]	Me	Et	*ent*-**8b** + *ent*-**9b**	66	49 : 51	94 (*ent*-**8b**), 91 (*ent*-**9b**)
2	Me	^{n}Pr	**8c** + **9c**	74	49 : 51	94 (**8c**), 92 (**9c**)
3	Me	^{n}Bu	**8a** + **9a**	73	49 : 51	90 (**8a**), 91 (**9a**)
4[e]	Me	^{n}Pent	**8d** + **9d**	71	49 : 51	90 (**8d**), 92 (**9d**)
5	Me	^{n}Hex	**8e** + **9e**	67	49 : 51	90 (**8e**), 92 (**9e**)
6[e]	Et	^{n}Pr	**8f** + **9f**	66	49 : 51	98 (**8f**), 97 (**9f**)
7[e]	Et	^{n}Bu	**8g** + **9g**	67	49 : 51	96 (**8g**), 95 (**9g**)
8	Me	$(CH_2)_2{}^i$Pr	**8h** + **9h**	66	52 : 48	83 (**8h**), 91 (**9h**)

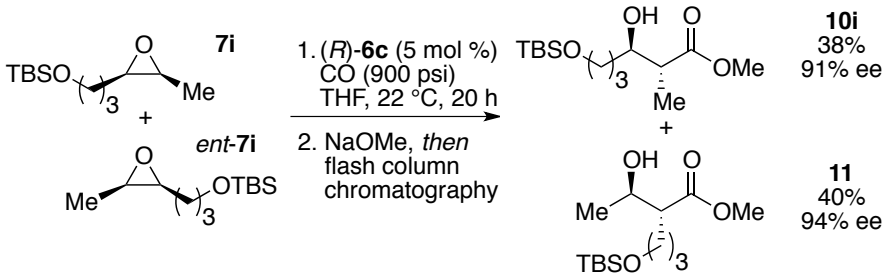
[a]Reaction conditions: [epoxide] = 0.5 M, 22 °C, 20 h. Yields are of isolated, combined β-lactones **8** and **9**. All reactions gave full conversion by GC analysis. [b]Determined *via* GC analysis from crude reaction mixture. [c]Enantiomeric excess determined by GC analysis. [d](*S*)-**6c** was used. [e](*R*)-**6c** (8 mol %) used. Catalysts (*R*)- and (*S*)-**6c** were generated *in situ* ($L_nAlCl + NaCo(CO)_4$).

importantly, **8** and **9** both showed excellent levels of enantioenrichment in the case of methyl-substituted epoxides (R^1 = Me) bearing linear or branched alkyl-groups as R^2

(entries 1-5, and 8). *Racemic* ethyl-substituted epoxides **7f** and **7g** (R^1 = Et) required slightly higher catalyst loadings, but also formed β-lactones **8** and **9** with exceptionally high degrees of enantiomeric excess (entries 6 and 7).

Overall, the results obtained with (*R*)-**6c** (Table 3.5) were reminiscent of those seen before with (*R*)-**6b** (Table 3.4). A significant difference, however, is that (*R*)-**6c** forms the two *trans*-β-lactone products **8** and **9** in a ratio of approximately 1 : 1, and both β-lactones show excellent enantiomeric excess exceeding 90% ee (β-lactone **8h** being the only exception). With catalyst (*R*)-**6b**, the less desired lactone **9** was the prevailing product and generally showed <86% ee. Nevertheless, catalysts (*R*)-**6b** and (*R*)-**6c** are complementary. (*R*)-**6b** is the catalyst of choice if highly enantioenriched lactones **8** (>94% ee) and the corresponding propionate aldol-type products **10** are desired. (*R*)-**6b**, on the other hand, provides access to both β-lactones in highly enantioenriched form (usually > 90% ee). These two lactones can also be transformed into enantioenriched aldol-type compounds (*vide infra*).

As before, the resulting lactones **8** and **9** were not readily separable *via* silica gel column chromatography. Consequently, mixtures of the two lactones were isolated in all cases in good yield. This, however, is of little concern if one is interested in the corresponding aldol-type products. Methyl-substituted β-lactones **8 a-e**,**h-i** and **9a-e**,**h-i** can still be separated from one another by converting them into the corresponding methyl-ester derivatives. One example for this is given in Equation 3.1 for *racemic* epoxide **7i**.



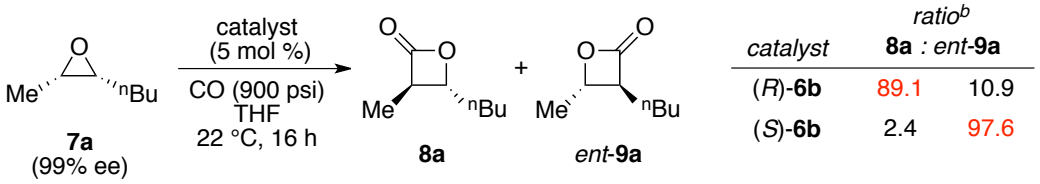
(3.1)

Epoxide **7i** first underwent regiodivergent carbonylation using (*R*)-**6c**. Using a one-pot sequence, the resulting β-lactones were ring-opened to the corresponding methyl-ester **10i** and **11**, which subsequently were isolated individually. As a result, two highly enantioenriched *anti*-aldol-type products were obtained from a single substrate using (*R*)-**6c**.

3.3.4 Detailed Investigation of the Regiodivergent Carbonylation of Racemic cis-Epoxides Using Catalyst (R)-6b

Having established the scope of this transformation for a variety of *racemic cis*-epoxides, the course of the reaction and factors responsible for its outcome were investigated next. As mentioned before, a regiodivergent reaction would explain the results obtained. A prerequisite for such a reaction would be that (*R*)-**6b** carbonylates both enantiomers of a given epoxide **7** with high and opposing regioselectivities. To confirm this hypothesis, highly enantioenriched **7a** was synthesized and carbonylated with either enantiomer of catalyst **6b** (Scheme 3.4).

As Scheme 3.4 shows, carbonylation of enantioenriched **7a** occurred with high and opposing regioselectivities when using (*R*)- and (*S*)-**6b**. Interestingly, the two enantiomers of **6b** showed some degree of a matched/mismatched pair with **7a**. (*R*)-**6b** carbonylated **7a** only with a regioselectivity of 8.2 : 1 with regard to **8a** and *ent*-**9a**.



catalyst	ratio[b] 8a : ent-9a	
(*R*)-**6b**	89.1	10.9
(*S*)-**6b**	2.4	97.6

Scheme 3.4 Regioselectivity in the carbonylation of enantioenriched epoxide 7a using catalysts (*R*)- and (*S*)-6b Both reactions gave >95% conversion (GC analysis), and ratios were determined *via* ^{1}H NMR analysis of crude reaction mixture. Catalysts (*R*)- and (*S*)-**6b** were generated *in situ* ($L_nAlCl + NaCo(CO)_4$).

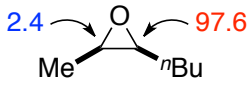
carbonylated **7a** only with a regioselectivity of 8.2 : 1 with regard to **8a** and *ent*-**9a**. Contrary to that, (*S*)-**6b** gave a much better ratio of 1 : 41 in favor of *ent*-**9a**. The same result, namely a ratio of 1 : 41 favoring **9a**, should be obtained if (*R*)-**6b** were to react with enantiopure *ent*-**7a**. Consequently, (*R*)-**6b** fulfills the requirement necessary for a regiodivergent reaction, namely providing high and opposing regioselectivities.

The experiments performed in Scheme 3.4 also revealed that (*R*)-**6b** displayed different levels of chemoselectivity when reacting with **7a** vs. *ent*-**7a**. The reaction with **7a** produced circa twice as much ketone side products, 2- and 3-heptanone, as the one with *ent*-**7a**. The formation of ketone is a consequence of unproductive isomerization reactions of the epoxide.[15d] In addition, **7a** produced 2- and 3-heptanone in approximately a 1 : 1 ratio, whereas *ent*-**7a** gave a ratio of circa 1 : 4. These findings explain the observed accumulation of 3-heptanone relative to 2-heptanone in the reaction of *racemic* **7a** with (*R*)-**6b** (*vide infra*, Figure 3.3). Moreover, these results seem to indicate that ketone formation is an inherent property of catalysts such as (*R*)-**6b**, and less the result of catalyst degradation.

The results from Scheme 3.4 also allow for two more conclusions. First, (*R*)-**6b** can be used to regioselectively carbonylate enantioenriched *cis*-epoxides **7**. Secondly,

the data in Scheme 3.4 allows calculation of the theoretically expected ratio of regioisomers and enantiomeric ratios for **8a** and **9a** in the regiodivergent carbonylation of *racemic* **7a** using (*R*)-**6b** (Figure 3.2).

7a



ent-**7a**

Regioselectivity of (*R*)-**6b** in the carbonylation of **7a** and *ent*-**7a** (data taken from Scheme 3.4)

Theoretical er for **8a** when using (*R*)-**6b**: 89.1 : 2.4 = 97.4 : 2.6 (94.8% ee)

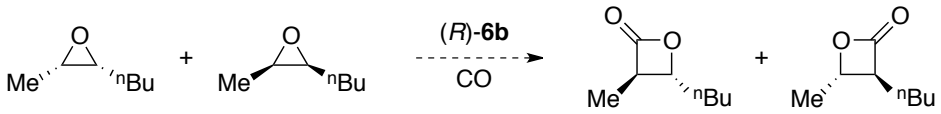
Theoretical er for **9a** when using (*R*)-**6b**: 97.6 : 10.9 = 90.0 : 10.0 (80.0% ee)

Calculation of theoretical ratio of regioisomers **8a** : **9a** when using (*R*)-**6b**:

ratio of **8a** : **9a** is (89.1 + 2.4) : (97.6 + 10.9) = 45.8 : 54.2

Figure 3.2 Calculation of the theoretical enantiomeric ratio (er) and ratio of regioisomers for the reaction of *racemic* epoxide 7a with catalyst (*R*)-6b

The thus obtained theoretical values were then compared to the experimental data (Scheme 3.5). Good agreement between theoretically predicted and experimentally observed results was noted as far as the ratio of regioisomers **8a** and **9a** and



7a *ent*-**7a** **8a** **9a**

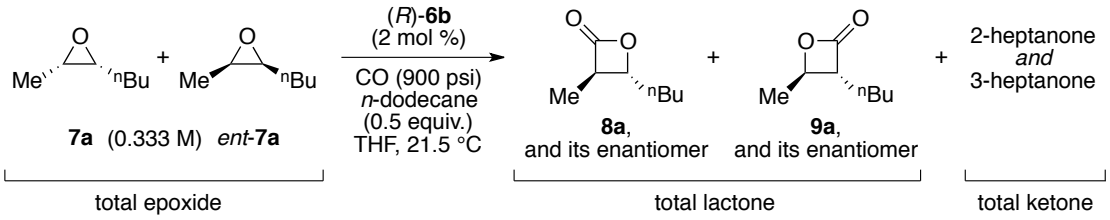
theoretical ratio **8a** : **9a**	45.8 : 54.2
experimentally observed ratio **8a** : **9a**	44.7 : 55.3
theoretical er of **8a**	97.4 : 2.6
experimentally observed er of **8a**	97.3 : 2.7
theoretical er of **9a**	90.0 : 10.0
experimentally observed er of **9a**	91.6 : 8.4

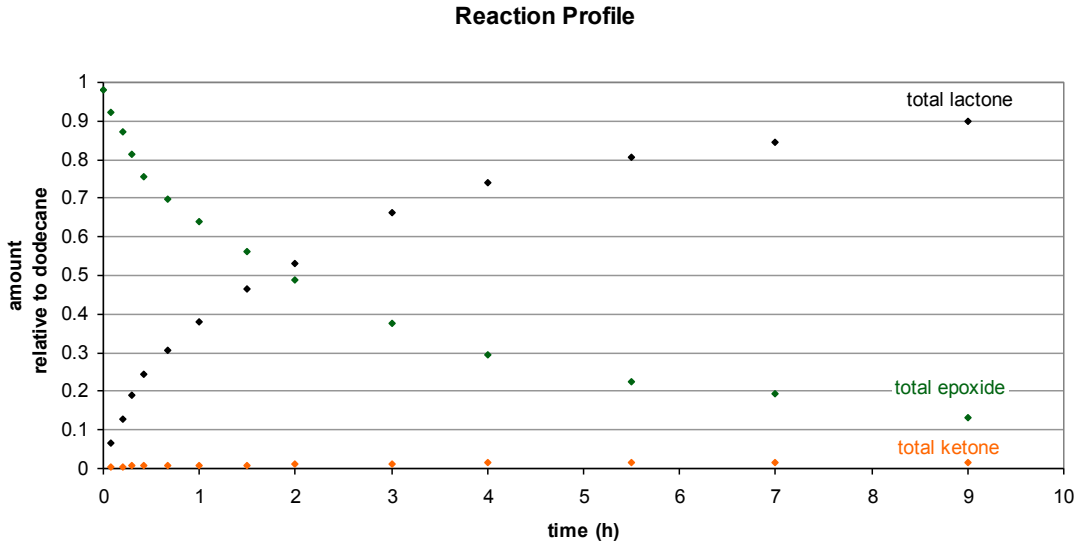
Scheme 3.5 Predicted and experimentally observed values for enantiomeric ratio (er) and ratio of regioisomers in the regiodivergent carbonylation of *racemic* epoxide 7a using catalyst (*R*)-6b Predicted values taken from **Figure 3.2**

enantiomeric ratio of **8a** are concerned. The enantiomeric ratio of **9a** deviates from the predicted value to a greater extent, and is higher than expected. This deviation can be attributed to the small amounts of ketone side product formed during the reaction. Since both enantiomers of the epoxide give rise to different amounts of ketone, it seems plausible that this can affect the enantiomeric ratios of **8a** and **9a** to different extents, and lead to deviations from the theoretically predicted values.

In a next step, the carbonylation of *racemic* **7a** with (*R*)-**6b** was monitored in detail using GC analysis. The resulting data (Figure 3.3) showed that (*R*)-**6b** consumed both enantiomers of the epoxide with comparable activity, with *ent*-**7a** reacting faster than **7a** by a factor of approximately 4 (*vide infra*). This observation rules out a transient kinetic resolution of the epoxide. Small amounts of ketone side products were also detected, and steadily increased as the reaction progressed. Interestingly, the two ketone products, 2- and 3-heptanone, are formed in unequal amounts, with 3-heptanone being the major species especially at later stages of the reaction. Different levels of chemoselectivity in the carbonylation reactions of **7a** and *ent*-**7a** with (*R*)-**6b** rationalize this observation, i.e. one enantiomer of the epoxide is more prone to giving ketone side-products than the other (*vide supra*).

Moreover, the collected data indicated that **9a**, the β-lactone preferentially formed by (*R*)-**6b** from *ent*-**7a** (Scheme 3.4 and Figure 3.4), is the lactone that is formed fastest and initially in >90% ee. Lactone **8a**, on the other hand, is produced slower and at first only with <80% ee. However, as the reaction progressed more of the other epoxide enantiomer **7a** was consumed, which causes the enantiomeric ratio of **9a** to slowly deteriorate. As shown in Figure 3.4, this is due to the fact that **3a** gives rise to





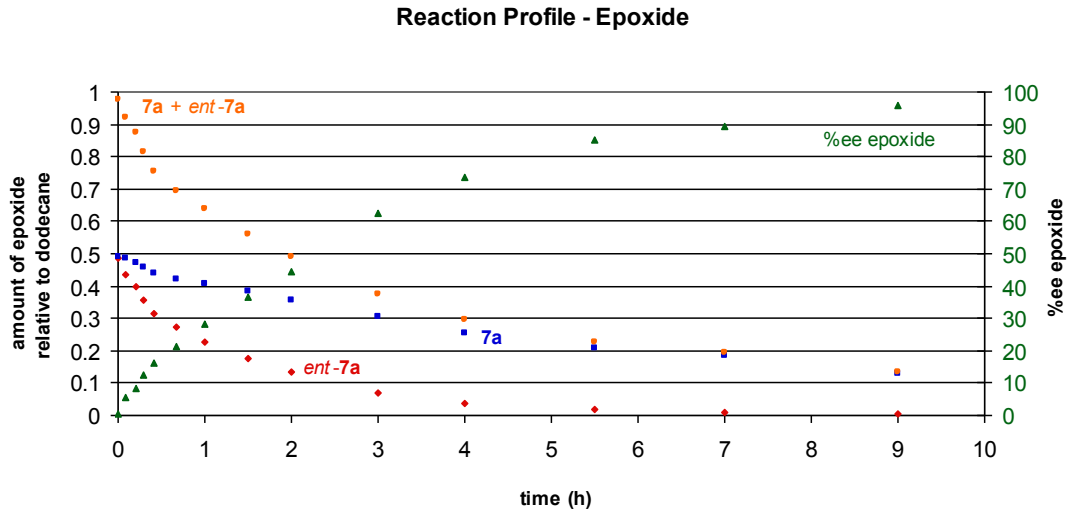
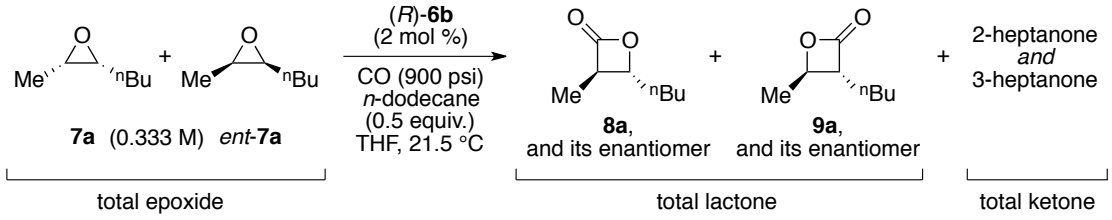
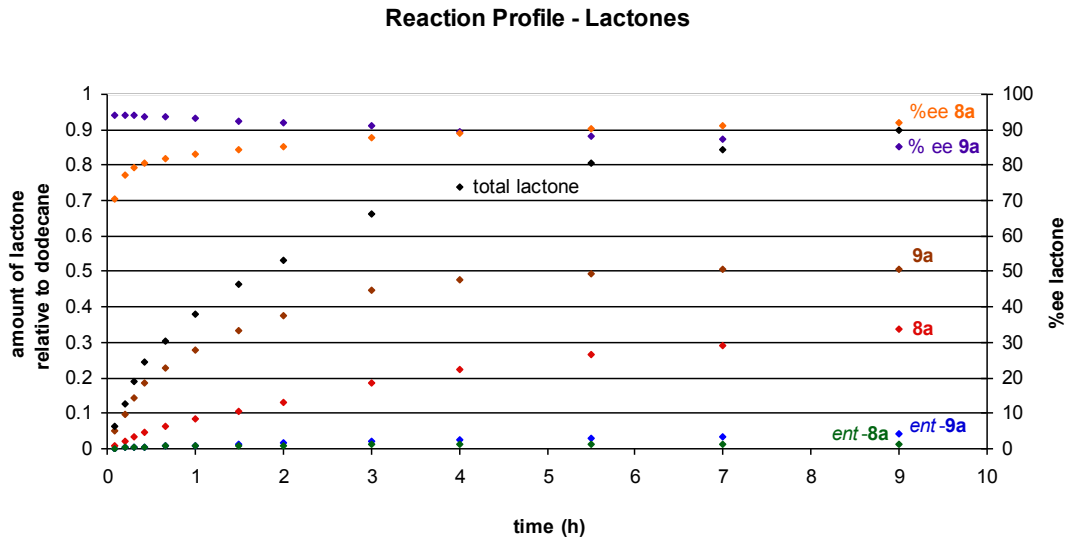


Figure 3.3 Reaction profiles of major species present in the regiodivergent carbonylation of *racemic* epoxide 7a using catalyst (*R*)-6b





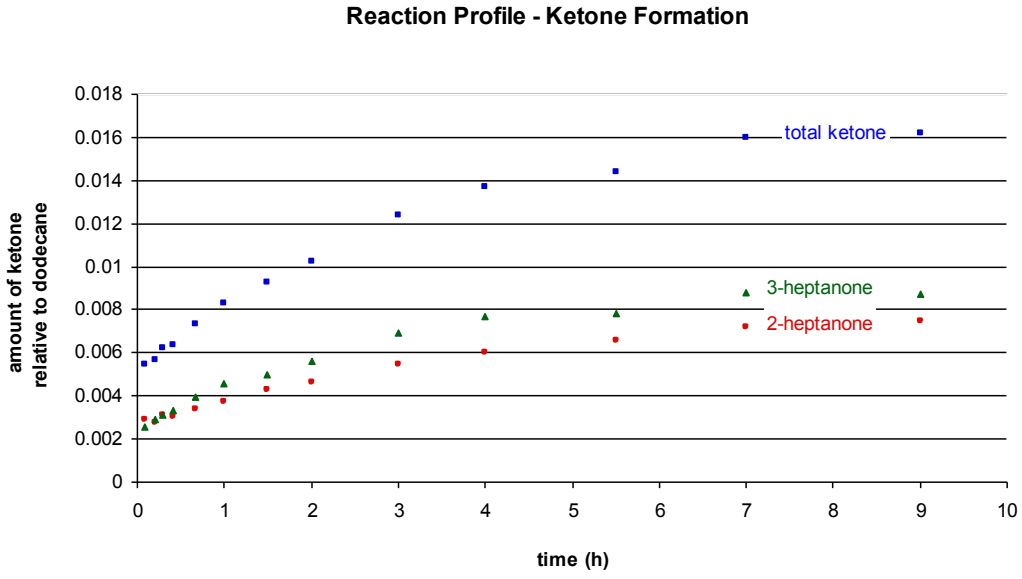


Figure 3.3 (continued)

8a and small amounts of *ent*-**9a**. Consequently, the %ee of **8a** steadily improves as that of **9a** declines, until **8a** reaches the excellent %ee that is observed upon completion of the reaction. Figure 3.4 summarizes most of the data discussed so far for the regiodivergent carbonylation of *racemic* **7a** using (*R*)-**6b**.

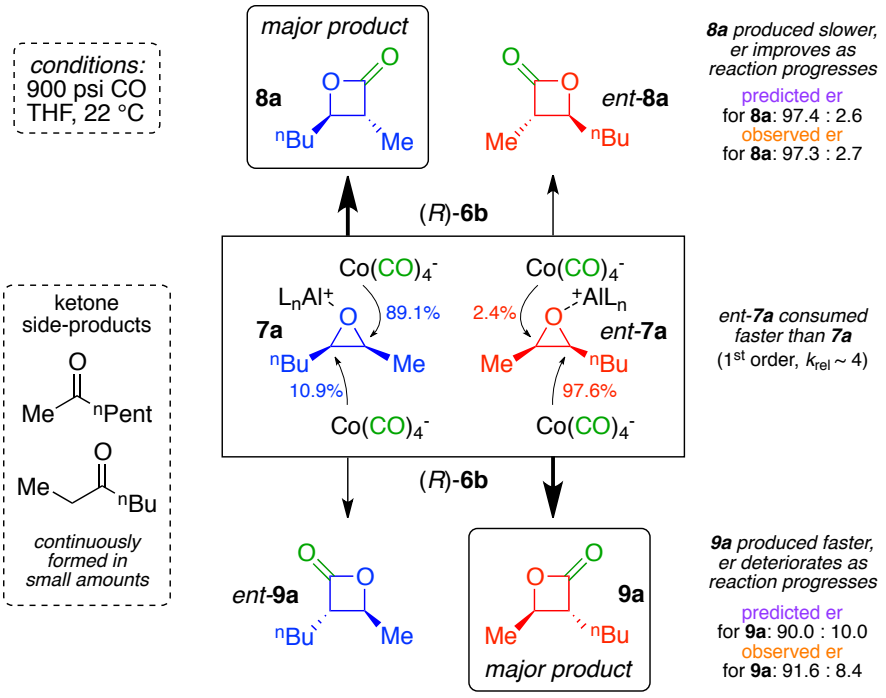


Figure 3.4 Detailed analysis of the regiodivergent carbonylation of *racemic* epoxide 7a with catalyst (*R*)-6b

Monitoring the reaction of *racemic* **7a** with (*R*)-**6b** also allowed for an approximation of the selectivity factor *s* with regard to the epoxide. These data can be estimated by plotting conversion of epoxide against its enantiomeric excess over the course of the reaction. The distribution of the data points in the resulting plot varies in a characteristic way depending on the selectivity factor *s* and the reaction order in substrate in the selectivity-determining step.[32] In case of the reaction of *racemic* **7a** with (*R*)-**6b** (Figure 3.5), the experimental plot resembled graphs that are associated

with a first order dependence in substrate. This is an interesting observation because previous mechanistic studies[16b] showed that salen-based carbonylation catalysts convert terminal epoxides with zero order dependence in the rate law. Moreover, a simulated curve representing a first order dependence and a selectivity factor *s* of ca. 4 adequately reproduced the experimental data points. Consequently, it seems reasonable to assume that the order in epoxide in the selectivity-determining step is 1

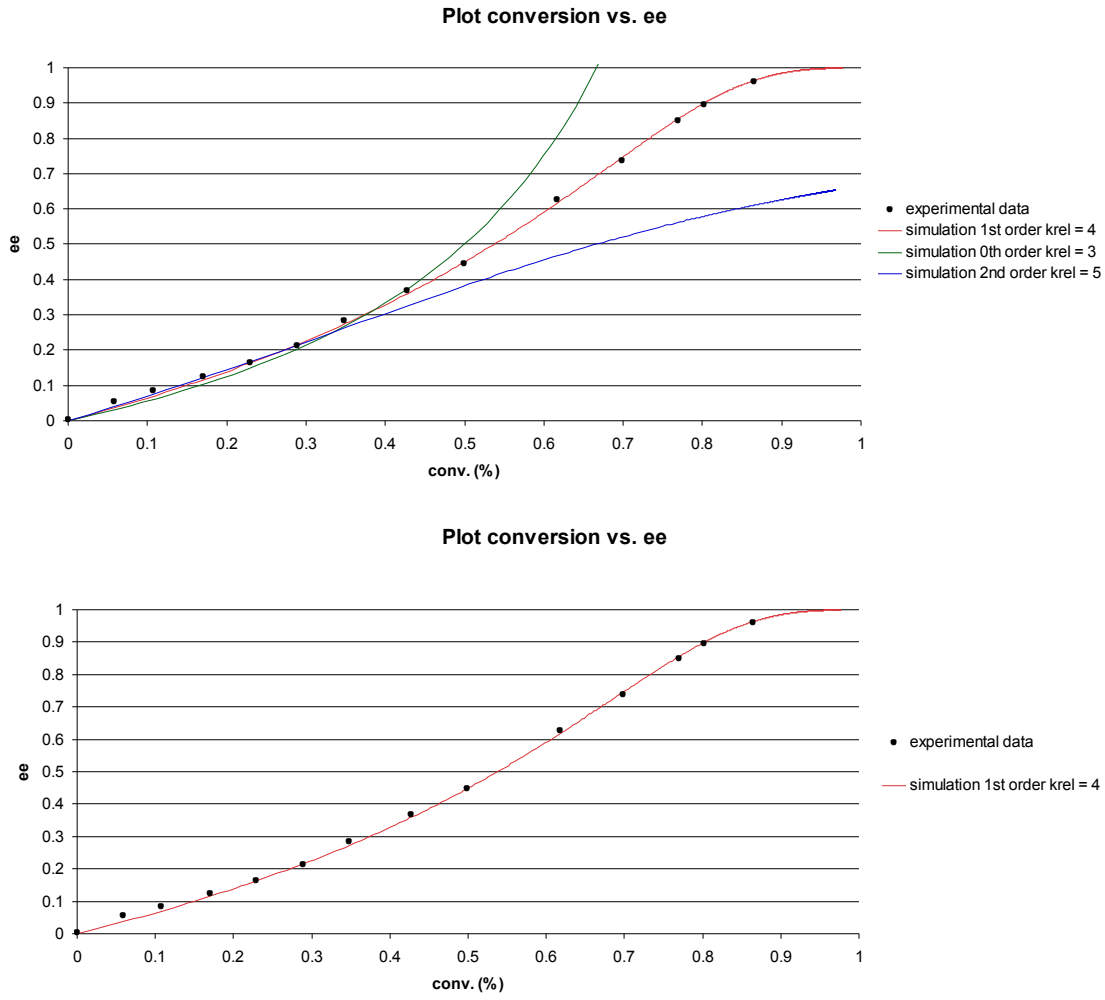


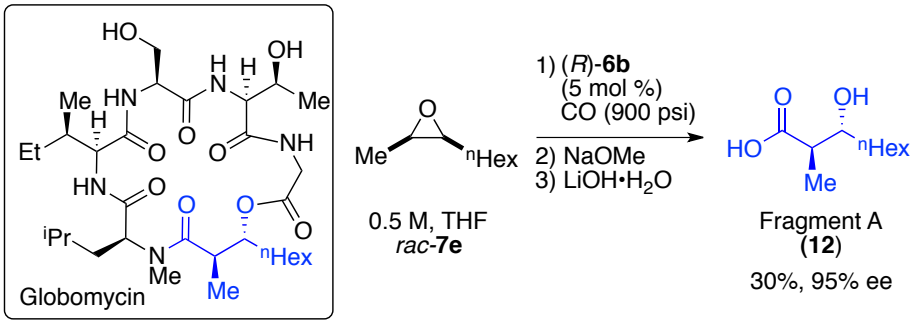
Figure 3.5 Experimentally determined data points for the variation of ee of unreacted epoxide relative to its conversion, and comparison to theoretical graphs for (a) zeroth-, (b) first-, and (c) second-order reactions in epoxide. The data points were aquired from the reaction of *racemic* **7a** with (*R*)-**6b**. The simulated graphs were calculated using the equations given in reference 32.

throughout most of the reaction, and that (*R*)-**6b** displays a selectivity factor *s* (k_{rel}) of approximately 4 in the regiodivergent carbonylation of *racemic* **7a**.

Lastly, this finding indicates again that an efficient classical kinetic resolution is not feasible with (*R*)-**6b** for *racemic* epoxides **7**.

3.3.5 Application of Regiodivergent Carbonylation to the Synthesis of Fragment A of Globomycin

Lastly, to demonstrate the applicability of the regiodivergent carbonylation methodology catalyst (*R*)-**6b** was used to synthesize Fragment A (**12**) of Globomycin[33] starting from *racemic* epoxide **7e** (Scheme 3.6). Globomycin is a promising antibiotic against Gram-negative bacteria and also shows the ability to act as a specific inhibitor of certain signal peptidases.[33] Furthermore, it was found that the activity of Globomycin depends strongly on the actual length of the alkyl chain in Fragment A.[34]



Scheme 3.6 Synthesis of Fragment A (12) of Globomycin using regiodivergent carbonylation

The desired fragment **12** was obtained in 30% yield starting from **7e**, and its enantiomeric excess of 95% ee compared favorably to the 92% ee reported in the literature for this compound.[33] What is even more important is that regiodivergent carbonylation is well suited to deliver derivatives of **12** with comparable

enantioselectivities as was seen in Encouraged by the screening results, the scope of this reaction using a variety of *racemic cis*-disubstituted epoxides **7** and catalyst (*R*)-**6b** was investigated next (Table 3.4). The resulting lactones **8** and **9** all showed high levels of enantioenrichment, but none of them could be separated quantitatively using flash column chromatography.

Table 3.4 and Table 3.5. The literature procedure comes short in this regard.[34] Moreover, regiodivergent carbonylation can deliver two highly enantioenriched derivatives of Fragment A in just one step if catalyst (*R*)-**6c** is used. This subsequently would allow for the rapid assembly of a library of Fragment A-analogs for structure-activity relationship studies. Overall, this application showcases the strength of regiodivergent carbonylation as a fast and economical means to generate molecular diversity, which is often needed in medicinal chemistry.

3.4 Conclusion

In conclusion, two new enantiopure carbonylation catalysts (*R*)-**6b** and (*R*)-**6c** based on salen-frameworks were reported. (*R*)-**6b** and (*R*)-**6c** were applied to the enantioselective desymmetrization of aliphatic *meso* epoxides and the regiodivergent carbonylation of *racemic cis*-disubstituted epoxides (Figure 3.6).

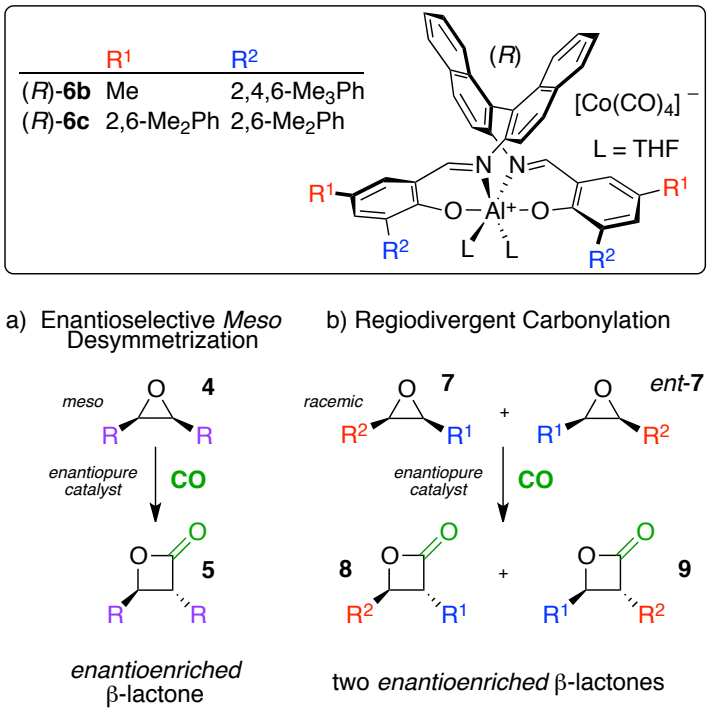


Figure 3.6 Catalysts and carbonylation reactions investigated for the synthesis of enantioenriched *trans*-β-lactones from either *meso* (a) or *racemic cis*-epoxides (b)

In both transformations, the two catalysts showed excellent levels of enantiomeric induction for a large variety of epoxides. The products are highly enantioenriched *trans*-β-lactones, which can be further elaborated to the corresponding *anti*-aldol-type products in a one-pot sequence. Both classes of compounds are not readily accessible with other methodologies. The effectiveness of (*R*)-**6b** and (*R*)-**6c** in inducing enantioenrichment was attributed to the *cis*-α coordination geometry of the ligand

around the Lewis acidic metal ion. Given that regiodivergent reactions based on S_N2-reactions are exceedingly rare, the occurrence and progression of the regiodivergent carbonylation reaction using *racemic* epoxide **7a** and catalyst (*R*)-**6b** was studied in detail. The two enantiomers of **7a** were shown to react with comparable rates, but were carbonylated with opposing regioselectivities. This finding was independently confirmed by carbonylating enantiopure **7a** with either enantiomer of catalyst **6b**. Lastly, regiodivergent carbonylation was applied to the synthesis of an important fragment of Globomycin. This example demonstrated the potential of regiodivergent carbonylation to generate a variety of derivatives for structure-activity relationship studies with comparatively little synthetic effort.

3.5 Experimental Procedures

3.5.1 General Considerations

Methods and instruments

Unless stated otherwise all synthetic manipulations were carried out using standard Schlenk techniques under a nitrogen atmosphere or in an MBraun Unilab glovebox under an atmosphere of purified nitrogen. Reactions were carried out in oven-dried glassware cooled under vacuum. High-pressure reactions were performed in a custom-designed and -fabricated, six-chamber, stainless steel, high-pressure reactor.[35] The reactor design allowed for incorporation of six 2 fluid dram glass vials. IR spectra were recorded on a Nicolet 380 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300, 400 or 500 MHz instrument at 22° C (unless indicated otherwise) with shifts reported relative to the residual solvent peak ($CDCl_3$: 7.26 ppm (^{1}H), and 77.16 ppm (^{13}C); C_6D_6: 7.16 ppm (^{1}H) and 128.06 ppm (^{13}C); THF-d_8: 3.58 ppm (^{1}H) and 67.57 ppm (^{13}C)). ^{19}F NMR spectra were recorded on a Varian 400 MHz instrument with shifts referenced to an external standard of neat $CFCl_3$ (0 ppm). NMR solvents were purchased from Cambridge Isotope Laboratories and stored over activated 4Å molecular sieves (C_6D_6) or K_2CO_3 ($CDCl_3$). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. GC analyses were performed on a Hewlett Packard 6890 gas chromatograph equipped with a Supelco b-Dex120 and a Supelco b-Dex225 column, and a flame ionization detector. Helium (Airgas, UHP grade) was used as carrier gas. HRMS analyses were performed at the

Mass Spectrometry Laboratory at the University of Illinois at Urbana-Champaign. Elemental analyses were performed at Midwest Microlab, LLC.

Chemicals

Anhydrous 1,4-dioxane, 1,2-dimethoxyethane (DME) and tetrahydropyran (THP) were purchased from Sigma-Aldrich and degassed *via* three freeze-pump-thaw cycles prior to use. Anhydrous toluene, dichloromethane, hexanes and tetrahydrofuran were purchased from Fischer Scientific and sparged vigorously with nitrogen for 40 minutes prior to first use. The solvents were further purified by passing them under nitrogen pressure through two packed columns of neutral alumina (tetrahydrofuran was also passed through a third column packed with activated 4Å molecular sieves) or through neutral alumina and copper(II) oxide (for toluene and hexanes). Tetrahydrofuran and dichloromethane were degassed *via* three freeze-pump-thaw cycles prior to use. Diethylether was dried over sodium/benzophenone and degassed *via* three freeze-pump-thaw cycles prior to use. Pentane and cyclohexane were dried over phosphor(V)oxide and degassed *via* three freeze-pump-thaw cycles prior to use. Triethylamine was dried over calcium hydride and degassed *via* three freeze-pump-thaw cycles prior to use. *n*-Dodecane and all epoxides used in this study were dried over calciumhydride and degassed *via* three freeze-pump-thaw cycles prior to use. All non-dried solvents used were reagent grade or better and used as received.

Carbon monoxide (Airgas, 99.99% min. purity) was used as received. All other chemicals were purchased from Aldrich, Alfa-Aesar or GFS Chemicals, and used as received. Flash column chromatography was performed with silica gel (particle size

40-64 μm, 230-400 mesh) using either mixtures of ethyl acetate and hexanes or mixtures of diethylether and pentane as eluent.

[(*S*,*S*)-salcyAl(THF)$_2$]$^+$[Co(CO)$_4$]$^-$ ((*S*,*S*)-**1**, (*S*,*S*)-salcy = (*S*,*S*)-*N*,*N*′-*bis*(3,5-di-*tert*-butyl-salicyl-idene)-1,2-cyclohexanediamine),[16] (*R*)-^{t}BuBinamAlCl (precursor to **2a**, (*R*)-^{t}BuBinam = (*R*)-*N*,*N*′-*bis*(2-hydroxy-3,5-di-*tert*-butylbenzylidene)-1,1'-binaphthyl-2,2'-diamine),[26] NaCo(CO)$_4$,[36] *rac*-(2*R*,3*S*)-2,3-diethyloxirane (*rac*-**4c**),[37] *rac*-(2*R*,3*S*)-2,3-dipropyloxirane (*rac*-**4a**),[38] *rac*-(2*R*,3*S*)-2,3-dibutyloxirane (*rac*-**4d**),[39] (*Z*)-oct-4-ene-1,8-diylbis(4-methylbenzenesulfonate) (*rac*-**SM1**),[40] *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane (*rac*-**7a**),[41] *rac*-(2*R*,3*S*)-2-ethyl-3-propyloxirane (*rac*-**7f**),[42] *rac*-(2*R*,3*S*)-2-butyl-3-ethyloxirane (*rac*-**7g**),[43] and the precursors to (*S*,*S*)-**15a**,[21] (*S*,*S*)-**15b**,[21] (*S*,*S*)-**15c**[21] were prepared according to literature procedures.

Racemic mixtures of β-lactones **8a**-**i** and **9a**-**i** were synthesized using [ClTPPAl(THF)$_2$]$^+$[Co(CO)$_4$]$^-$ (ClTPP = *meso* tetra(4-chlorophenyl)porphyrinato).[44]

3.5.2 Synthetic Procedures

3.5.2.1 General Procedures

General procedure A: Epoxidation of alkenes to epoxides using *m*CPBA

*m*CPBA (Aldrich, ≤ 77%) was added in portions at 0 °C to a solution of the corresponding alkene in DCM and the resulting mixture was stirred at the same temperature until TLC analysis indicated complete consumption of the alkene. After destroying excess *m*CPBA by adding aqueous $NaHSO_3$ at 0 °C, the reaction mixture was filtered, the organic phase washed with $NaHCO_3$ (sat., aq., 3x), dried with sodium

sulfate, filtered and concentrated under reduced pressure. The residue was purified either *via* distillation or flash column chromatography.

General procedure B: Carbonylation of epoxides using (*R*)-6b and (*R*)-6c

In a glove box, a 2 fluid dram glass vial equipped with a Teflon-coated magnetic stir bar was charged with the appropriate pre-catalyst, $NaCo(CO)_4$, and the appropriate solvent. After 1 minute of stirring at 22 °C, the vial was placed in a custom-made 6-well high-pressure reactor which itself was placed in a glove box freezer (-34 °C) for 30 minutes. The appropriate epoxide (also cooled to -34 °C) was then added to the vial, the reactor removed from the freezer, subsequently sealed, taken out of the glove box, placed in a well-ventilated hood and pressurized with carbon monoxide (900 psi). It is important to keep the temperature of the reactor below 0 °C once it is removed from the freezer to minimize isomerization of the epoxide to ketone products. The reactor was then sealed again, placed in a 22 °C water bath (unless noted otherwise) and the reaction mixture stirred for the time indicated. The reactor was then carefully vented in a well-ventilated hood and the product isolated as indicated.

General procedure C: Derivatization of β-hydroxymethylesters with trifluoroacetic anhydride for GC analysis

The corresponding β-hydroxymethylester (ca. 5-10 mg) was dissolved in DCM (1 ml). Three equivalents of pyridine were added, followed by slow addition of three equivalents of trifluoroacetic anhydride at 0 °C, and the resulting reaction mixture was stirred at 22 °C. Hydrochloric acid (1M, aq.) was added as soon as TLC analysis

indicated full conversion of starting material. The resulting phases were separated, the organic phase dried with sodium sulfate, and subsequently passed through a short plug of silica gel using diethylether as eluent. The eluate was then subjected to GC analysis.

3.5.2.2 Synthesis of Starting Materials

(*Z*)-1,8-Bis(2,2,2-trifluoroethoxy)oct-4-ene (SM1)

2,2,2-Trifluoroethanol (1.51 g, 15.1 mmol) was added dropwise to a mixture of sodium hydride (Aldrich, 95%, dry, 0.480 g, 20.0 mmol) and THF (10 ml) at 0 °C. After stirring for 1 h at 22 °C, a solution of (*Z*)-oct-4-ene-1,8-diylbis(4-methylbenzene-sulfonate)[8] in THF (5 ml) was added at 0 °C, and the resulting mixture refluxed for 12 h. The reaction mixture was then cooled to 22 °C, H_2O was added, followed by extraction of the aqueous phase with Et_2O (3x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to afford **SM1** (1.38 g, 85%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.38 (ddd, *J* = 5.7, 4.4, 1.1 Hz, 2H), 3.79 (q, *J* = 8.8 Hz, 4H), 3.59 (t, *J* = 6.4 Hz, 4H), 2.12 (td, *J* = 7.2, 5.4 Hz, 4H), 1.67 (dt, *J* = 7.8, 6.5 Hz, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 129.7, 124.3 (d, *J* = 281.4 Hz), 72.2, 68.4 (q, *J* = 33.8 Hz), 29.5, 23.4. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -74.4 (t, *J* = 8.8 Hz). **IR** (neat, cm^{-1}): 2935, 1441, 1275, 1133, 966, 827. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{18}F_6NaO_2^+$ ($M + Na^+$) 331.1103, found 331.1110.

2,3-Bis(3-(2,2,2-trifluoroethoxy)propyl)oxirane (4e)

Following general procedure A, (*Z*)-1,8-bis(2,2,2-trifluoroethoxy)oct-4-ene (**SM1**, 1.28 g, 4.15 mmol) was reacted with *m*CPBA (1.41 g) in DCM (10 ml) to give **4e** (1.19 g, 88%) as a colorless liquid. **^{1}H NMR** (400 MHz, C_6D_6): δ 3.23 (q, *J* = 8.8 Hz, 4H), 3.16–3.05 (m, 4H), 2.62–2.57 (m, 2H), 1.52–1.28 (m, 8H). **^{13}C NMR** (101 MHz, C_6D_6): δ 124.7 (d, *J* = 279.6 Hz), 72.0, 68.1 (q, *J* = 33.4 Hz), 56.2, 27.0, 24.6. **^{19}F NMR** (376 MHz, C_6D_6): δ -74.2 (t, *J* = 8.9 Hz). **IR** (neat, cm^{-1}): 2935, 1444, 1275, 1131, 966, 826. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{19}F_6O_3^+$ ($M + H^+$) 325.1233, found 325.1245.

***rac*-(2*S*,3*R*)-2-Ethyl-3-methyloxirane (*rac*-7b)**

Following general procedure A, (*Z*)-pent-2-ene (7.00 g, 99.8 mmol) was reacted with *m*CPBA (27.5 g) in DCM (100 ml) to give *rac*-**7b** (0.992 g, 12%) as a colorless liquid. The analytical data was in accordance with that reported in the literature.[45] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.02 (qd, *J* = 5.5, 4.2 Hz, 1H), 2.84 (td, *J* = 6.4, 4.2 Hz, 1H), 1.61–1.52 (m, 1H), 1.54–1.42 (m, 1H), 1.25 (d, *J* = 5.5 Hz, 3H), 1.01 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 58.3, 52.8, 21.0, 13.1, 10.5.

***rac*-(2*R*,3*S*)-2-Methyl-3-propyloxirane (*rac*-7c)**

Following general procedure A, (*Z*)-hex-2-ene (5.12 g, 60.8 mmol) was reacted with *m*CPBA (17.0 g) in DCM (135 ml) to give *rac*-**7c** (1.74 g, 29%) as a colorless liquid. The analytical data was in accordance with that reported in the literature.[46] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.01 (qd, *J* = 5.5, 4.3 Hz, 1H), 2.87 (td, *J* = 5.9, 4.1 Hz,

1H), 1.54–1.39 (m, 4H), 1.24 (d, J = 5.6 Hz, 3H), 0.96–0.93 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 57.0, 52.6, 29.6, 19.8, 14.1, 13.3.

***rac*-(2*R*,3*S*)-2-Methyl-3-pentyloxirane (*rac*-7d)**

Following general procedure A, (*Z*)-oct-2-ene (5.00 g, 44.6 mmol) was reacted with *m*CPBA (12.6 g) in DCM (100 ml) to give *rac*-**7d** (3.47 g, 61%) as a colorless liquid. The analytical data was in accordance with that reported in the literature.[47] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.99 (qd, J = 5.5, 4.4 Hz, 1H), 2.86–2.83 (m, 1H), 1.52–1.25 (m, 8H), 1.22 (d, J = 5.5 Hz, 3H), 0.87–0.85 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 57.2, 52.7, 31.8, 27.6, 26.20, 22.7, 14.0, 13.2.

***rac*-(2*S*,3*R*)-2-Hexyl-3-methyloxirane (*rac*-7e)**

Following general procedure A, (*Z*)-non-2-ene[17] (1.19 g, 9.43 mmol) was reacted with *m*CPBA (2.40 g) in DCM (18 ml) to give *rac*-**7e** (1.05 g, 78%) as a colorless liquid. The analytical data was in accordance with that reported in the literature.[48] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.04 (qd, J = 5.5, 4.3 Hz, 1H), 2.90 (td, J = 5.9, 4.2 Hz, 1H), 1.58–1.24 (m, 10H), 1.27 (d, J = 5.4 Hz, 3H), 0.91–0.87 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 57.3, 52.7, 31.9, 29.3, 27.7, 26.5, 22.7, 14.2, 13.3.

***rac*-(2*S*,3*R*)-2-Isopentyl-3-methyloxirane (*rac*-7h)**

6-Methylhept-2-yne (4.41 g, 40.0 mmol), Lindlar catalyst (Aldrich, 1.50 g), pentane (30 ml) and quinoline (freshly distilled, 1.65 g, 12.7 mmol) were placed in a Fisher-Porter tube, and the contents of the tube purged with nitrogen for 5 minutes. A

H_2-pressure of 32 psi was applied to the tube and the reaction mixture stirred at 22 °C until TLC analysis indicated complete disappearance of starting material (during this process the tube was repressurized with H_2-gas as necessary). The Fisher-Porter tube was carefully vented, then HCl (1 M, aq.) was carefully added and the reaction mixture filtered through a pad of celite. The organic phase was washed with HCl (1 M, aq., 2x), then dried with sodium sulfate, filtered and concentrated under reduced pressure.

Following general procedure A, the residue was reacted with *m*CPBA (12.2 g) in DCM (80 ml) to give *rac*-**7h** (1.22 g, 24%) as a colorless liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.04 (qd, *J* = 5.5, 4.2 Hz, 1H), 2.88 (td, *J* = 6.1, 4.2 Hz, 1H), 1.64–1.35 (m, 4H), 1.32–1.23 (m, 1H), 1.27 (d, *J* = 5.5 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 57.4, 52.8, 35.5, 28.0, 25.6, 22.7, 22.5, 13.3. **IR** (neat, cm^{-1}): 2957, 1468, 1389, 1065, 982, 804, 790. **HRMS** (ESI) *m/z* calculated for $C_8H_{17}O^+$ ($M + H^+$) 129.1274, found 129.1276.

(*Z*)-*Tert*-butyl(hex-4-en-1-yloxy)dimethylsilane (SM2)

(*Z*)-Hex-4-en-1-ol (0.955 g, 9.53 mmol) and 1-methyl-1*H*-imidazole (2.47 g, 30.1 mmol) were added to a solution of *tert*-butylchlorodimethylsilane (1.80 g, 11.9 mmol) in DCM (24 ml) at 0 °C. The reaction mixture was stirred for 24 h at 22 °C, then washed with water, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to give **SM2** (1.76 g, 86%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.49–5.35 (m, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.12–2.06 (m, 2H), 1.61–1.54 (m, 5H), 0.90 (s, 9H), 0.05 (s,

6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 130.3, 124.3, 62.8, 32.8, 26.1, 23.3, 18.5 12.9, -5.1. **IR** (neat, cm^{-1}): 2929, 2857, 1472, 1254, 1098, 833, 773. **Elemental analysis:** $C_{12}H_{26}OSi$ (214.42), calculated C 67.22, H 12.22; found C 67.04, H 11.97. No molecular ion peak was observed when performing EI-MS or ESI-MS analysis, consequently no HRMS data was acquired.

***rac*-*Tert*-butyldimethyl(3-((2*S*,3*R*)-3-methyloxiran-2-yl)propoxy)silane (*rac*-7i)**

Following general procedure A, (*Z*)-*tert*-butyl(hex-4-en-1-yloxy)dimethylsilane (**SM2**) (1.60 g, 7.46 mmol) was reacted with *m*CPBA (1.86 g) in DCM (20 ml) to give *rac*-**7i** (1.61 g, 94%) as a colorless liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.71–3.59 (m, 2H), 3.04 (td, *J* = 5.6, 4.3 Hz, 1H), 2.92 (td, *J* = 6.0, 4.1 Hz, 1H), 1.92–1.49 (m, 4H), 1.26 (d, *J* = 5.4 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 62.8, 57.0, 52.8, 29.8, 26.1, 24.3, 18.5, 13.3, -5.2. **IR** (neat, cm^{-1}): 2955, 2857, 1472, 1253, 1097, 833, 773. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{27}O_2Si^+$ ($M + H^+$) 231.1775, found 231.1777.

(*S*)-2-(Benzyloxy)heptan-3-one (SM3)

(*S*)-2-(Benzyloxy)-1-(pyrrolidin-1-yl)propan-1-one[49] (4.66 g, 20.0 mmol) was added to THF (70 ml), and the resulting mixture cooled to -78 °C. *n*-Butyllithium (Acros, 1.6 M, hexanes, 14.5 ml, 23 mmol) was added dropwise at -78 °C under vigorous stirring, and then the reaction mixture was stirred for 6 minutes at -78 °C. Ammonium chloride (sat., aq.) was added, and the aqueous layer extracted with Et_2O (2x). The combined organic layers were dried with sodium sulfate, filtered and

concentrated under reduced pressure. The residue was purified *via* flash column chromatography to give **SM3** (3.17 g, 72%) as a colorless liquid. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.31–7.14 (m, 5H), 4.45 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 3.85 (q, *J* = 6.9 Hz, 1H), 2.56–2.38 (m, 2H), 1.52–1.42 (m, 2H), 1.29–1.17 (m, 2H), 1.24 (d, *J* = 6.8 Hz, 3H), 0.82 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 213.2, 137.8, 128.6, 128.0, 127.9, 80.8, 72.0, 37.2, 25.5, 22.5, 17.6, 14.0. **IR** (neat, cm^{-1}): 2958, 2933, 2872, 1716, 1454, 1368, 1113, 734. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{20}O_2Na^+$ (M + Na^+) 243.1356, found 243.1358. **Specific rotation**: $[\alpha]^{22}_D$ = -49.7 (*c* = 1.1, $CHCl_3$).

(2*S*,3*S*)-2-(Benzyloxy)heptan-3-ol (SM4)

L-Selectride (Aldrich, 1.0 M, THF, 4.5 ml, 4.5 mmol) was added to a solution of (*S*)-2-(benzyloxy)heptan-3-one (**SM3**, 0.783 g, 3.55 mmol) in THF (12 ml) dropwise at -78 °C. After stirring for 2 h at -78 °C, ammonium chloride (sat., aq.) was added, and the aqueous layer extracted with Et_2O (2x). The combined organic layers were washed with $NaHCO_3$ (sat., aq.), dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to give **SM4** (0.483 g, 61%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29–7.19 (m, 5H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.37 (d, *J* = 11.5 Hz, 1H), 3.38–3.34 (m, 1H), 3.31 (q, *J* = 6.1 Hz, 1H), 2.47 (s, 1H), 1.43–1.22 (m, 6H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.83 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 138.5, 128.6, 128.0, 127.9, 78.6, 75.1, 71.1, 32.7, 27.9, 22.9, 15.7, 14.2. **IR** (neat, cm^{-1}): 2932, 2860, 1454, 1375,

1072, 1027, 733. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{23}O_2^+$ (M + H^+) 223.1693, found 223.1699. **Specific rotation**: $[\alpha]^{22}_D$ = +27.2 (*c* = 0.90, $CHCl_3$).

(2*S*,3*S*)-2-(Benzyloxy)heptan-3-yl 4-methylbenzenesulfonate (SM5)

(2*S*,3*S*)-2-(Benzyloxy)heptan-3-ol (**SM4**, 0.416 g, 1.87 mmol), 4-methylbenzene-1-sulfonyl chloride (1.00 g, 5.25 mmol), and pyridine (1.96 g, 24.7 mmol) were mixed and stirred at 40 °C for 5 h. The reaction mixture was allowed to cool to 22 °C, Et_2O was added and the organic phase was washed with HCl (1 M, aq., 2x). The organic layer was then dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to give **SM5** (0.632 g, 90%) as a colorless liquid, which was stored at -15 °C to prevent discoloration of the product. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.34–7.23 (m, 7H), 4.53 (qu, *J* = 4.2 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 3.66 (qd, *J* = 6.4, 4.4 Hz, 1H), 2.40 (s, 3H), 1.68 (dddd, *J* = 13.9, 9.9, 5.9, 3.8 Hz, 1H), 1.57–1.45 (m, 1H), 1.21–1.10 (m, 3H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.06–0.93 (m, 1H), 0.77 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.6, 138.4, 134.4, 129.7, 128.4, 127.9, 127.8, 127.7, 84.4, 74.6, 71.4, 28.7, 27.3, 22.5, 21.7, 14.6, 13.9. **IR** (neat, cm^{-1}): 2956, 2871, 1598, 1362, 1174, 1096, 904, 813. **HRMS** (ESI) *m/z* calculated for $C_{21}H_{28}O_4NaS^+$ (M + Na^+) 399.1603, found 399.1601. **Specific rotation**: $[\alpha]^{22}_D$ = -22.1 (*c* = 0.60, $CHCl_3$).

(2*S*,3*S*)-2-Hydroxyheptan-3-yl 4-methylbenzenesulfonate (SM6)

Palladium on carbon (Strem, 5% Pd, 0.352 g), methanol (15 ml), and (2*S*,3*S*)-2-(benzyloxy)heptan-3-yl 4-methylbenzenesulfonate (**SM5**, 0.498 g, 1.32 mmol) were placed in a Fisher-Porter tube and the contents of the tube purged with nitrogen for 5 minutes. A H_2-pressure of 32 psi was applied to the tube and the reaction mixture stirred at 22 °C until TLC analysis indicated complete disappearance of starting material (during this process the tube was repressurized with H_2-gas as necessary). The Fisher-Porter tube was carefully vented, Et_2O was added, and the resulting mixture filtered through celite. The filtrate was concentrated under reduced pressure and the residue purified *via* flash column chromatography to give **SM6** (0.309 g, 82%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 4.45 (dt, *J* = 7.3, 5.1 Hz, 1H), 3.84 (qd, *J* = 6.4, 5.1 Hz, 1H), 2.43 (s, 3H), 2.24 (s, 1H), 1.65 (dddd, *J* = 15.4, 7.8, 6.5, 4.9 Hz, 1H), 1.57–1.48 (m, 1H), 1.26–1.12 (m, 4H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.80 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 144.9, 134.2, 129.9, 127.9, 87.7, 68.2, 30.2, 26.9, 22.5, 21.7, 18.9, 13.9. **IR** (neat, cm^{-1}): 3531, 2957, 2872, 1356, 1173, 1096, 894, 813. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{23}O_4S^+$ ($M + H^+$) 287.1317, found 287.1312. **Specific rotation**: $[\alpha]^{22}_D$ = +4.4 (*c* = 3.9, $CHCl_3$).

(2*R*,3*S*)-2-Butyl-3-methyloxirane (7a)

A solution of (2*S*,3*S*)-2-hydroxyheptan-3-yl 4-methylbenzenesulfonate (**SM6**, 4.46 g, 15.6 mmol) in Et_2O (10 ml) was added to a suspension of sodium hydride (Aldrich, 95%, dry, 0.560 g, 23.3 mmol) in Et_2O (40 ml), and refluxed for 3 days.

Upon cooling to 0 °C, H_2O was added and the aqueous phase extracted with Et_2O (2x). The combined organic layers were dried with sodium sulfate, filtered and concentrated under reduced pressure. Distillation of the crude product mixture provided **7a** (0.861 g, 43%) as a colorless liquid. The analytical data was in accordance with that reported for *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane in the literature.[50] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.04 (qd, *J* = 5.5, 4.2 Hz, 1H), 2.90 (td, *J* = 5.8, 4.0 Hz, 1H), 1.56–1.32 (m, 6H), 1.26 (d, *J* = 5.5 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 57.1, 52.6, 28.7, 27.3, 22.6, 14.1, 13.2. **Specific rotation**: $[\alpha]^{22}_D$ = -8.1 (*c* = 0.53, $CHCl_3$).

The enantiomeric ratio (er) was determined to be >99 : 1 by GC analysis (b-Dex225 column) in comparison to authentic *racemic* material.

2',4',5,6'-Tetramethyl-[1,1'-biphenyl]-2-ol (SM7)

2-Bromo-4-methylphenol (freshly distilled, 2.33 g, 12.4 mmol) was added dropwise to a mixture of sodium hydride (Aldrich, 95%, dry, 0.380 g, 15.8 mmol) and THF (20 ml) at 0 °C, followed by stirring at 22 °C for 10 minutes. $Pd(acac)_2$ (0.170 g, 0.558 mmol, 4.50 mol %) was added, followed by mesitylmagnesium bromide (Aldrich, 1.0 M, THF, 18 ml), and the resulting mixture was refluxed for 12 h. Upon cooling to 0 °C, H_2O and then HCl (2 M, aq.) were added, and the resulting mixture was filtered through a pad of celite. The resulting phases were separated and the aqueous phase extracted with Et_2O (3x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to give **SM7**

(2.78 g, 99%) as an off-white solid. **MP** 66–67 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 2H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.83 (s, 1H), 4.49 (d, *J* = 0.9 Hz, 1H), 2.35 (s, 3H), 2.32 (s, 3H), 2.04 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 150.3, 138.0, 137.8, 132.0, 130.5, 129.9, 129.5, 128.8, 126.3, 114.9, 21.2, 20.7, 20.4. **IR** (neat, cm^{-1}): 3477, 2917, 1478, 1436, 1272, 1230, 1161, 1031, 819. **HRMS** (ESI) *m/z* calculated for $C_{16}H_{18}NaO^+$ ($M + Na^+$) 249.1250, found 249.1259.

2-Hydroxy-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-carbaldehyde (SM8)

Methylmagnesium bromide (Acros, 3 M, Et_2O, 6.5 ml, 20 mmol) is added slowly to 2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol (**SM7**, 3.78 g, 16.7 mmol) in THF (40 ml) at 0 °C. After warming to 22 °C, toluene (80 ml), triethylamine (2.76 g, 27.3 mmol) and paraformaldehyde (1.28 g, 42.6 mmol) were added, and the resulting reaction mixture stirred at 80 °C for 12 h. After cooling to 0 °C, H_2O and then HCl (2 M, aq.) were added, and the resulting phases were separated. The aqueous phase was extracted with Et_2O (2x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to afford **SM8** (3.32 g, 78%) as an off-white solid. **MP** 105–106 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.95 (s, 1H), 9.93 (s, 1H), 7.37 (d, *J* = 2.3 Hz, 1H), 7.18 (d, *J* = 2.2 Hz, 1H), 6.97 (s, 2H), 2.39 (s, 3H), 2.34 (s, 3H), 2.03 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 196.8, 156.9, 139.5, 137.4, 136.6, 132.9, 132.8, 129.8, 129.2, 128.3, 120.6, 21.3, 20.45, 20.44. **IR** (neat, cm^{-1}): 2917, 1643, 1454, 1320, 1224, 1103, 971, 850, 798, 742. **HRMS** (ESI) *m/z* calculated for $C_{17}H_{19}O^+$ ($M + H^+$) 255.1380, found 255.1383.

2,2'',6,6''-Tetramethyl-[1,1':3',1''-terphenyl]-4'-ol (SM9)

A solution of 2,4-dibromophenol (freshly sublimed, 3.80 g, 15.1 mmol) in THF (10 ml) was added dropwise to a mixture of sodium hydride (Aldrich, 95%, dry, 0.518 g, 21.6 mmol) and THF (38 ml) at 0 °C, followed by stirring at 22 °C for 10 minutes. $Pd(OAc)_2$ (0.277 g, 1.23 mmol, 8.17 mol %) was added, followed by 2,6-dimethylphenylmagnesium bromide (Aldrich, 1.0 M, THF, 40 ml), and the resulting mixture was refluxed for 12 h. Upon cooling to 0 °C, H_2O and then HCl (2 M, aq.) were added, and the resulting mixture was filtered through a pad of celite. The resulting phases were separated and the aqueous phase extracted with Et_2O (2x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography to give **SM9** (3.17 g, 70%) as a thick yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29–7.12 (m, 8H), 6.85 (t, J = 1.3 Hz, 1H), 4.68 (s, 1H), 2.16 (s, 6H), 2.15 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 151.2, 141.6, 137.9, 136.5, 134.8, 133.6, 130.4, 129.8, 128.5, 128.1, 127.4, 127.0, 126.5, 115.4, 21.1, 20.4. **IR** (neat, cm^{-1}): 3486, 2917, 1463, 1219, 1161, 828, 768. **HRMS** (ESI) *m/z* calculated for $C_{22}H_{22}NaO^+$ ($M + Na^+$) 325.1563, found 325.1563.

4'-Hydroxy-2,2'',6,6''-tetramethyl-[1,1':3',1''-terphenyl]-5'-carbaldehyde (SM10)

Methylmagnesium bromide (Acros, 3 M, Et_2O, 4.0 ml, 12.0 mmol) is added slowly to 2,2'',6,6''-tetramethyl-[1,1':3',1''-terphenyl]-4'-ol (**SM9**, 2.80 g, 9.26 mmol) in THF (20 ml) at 0 °C. After warming to 22 °C, toluene (39 ml), triethylamine (1.60 g, 15.8 mmol) and paraformaldehyde (0.810 g, 27.0 mmol) were added, and the

resulting reaction mixture stirred at 80 °C for 12 h. After cooling to 0 °C, H_2O and then HCl (2 M, aq.) were added, and the resulting phases were separated. The aqueous phase was extracted with Et_2O (2x). The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified *via* flash column chromatography followed by recrystallization from methanol to afford **SM10** (1.90 g, 62%) as a colorless solid. **MP** 111–112 °C (methanol). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 11.16 (s, 1H), 9.98 (s, 1H), 7.41 (d, *J* = 2.1 Hz, 1H), 7.23–7.13 (m, 7H), 2.12 (s, 12H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 196.9, 157.6, 139.9, 139.44, 139.44, 136.6, 136.4, 135.7, 133.3, 132.9, 130.2, 128.0, 127.7, 127.5, 120.9, 21.1, 20.6. **IR** (neat, cm^{-1}): 2917, 1651, 1451, 1266, 1197, 1082, 934, 767. **HRMS** (ESI) *m/z* calculated for $C_{23}H_{23}O_2^+$ ($M + H^+$) 331.1693, found 331.1688.

3.5.2.3 Synthesis and Metallation of Salen-Compounds

(*R*)-3,3''-(([1,1'-Binaphthalene]-2,2'-diylbis(azanylylidene))bis(methanylylidene))-bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol) ((*R*)-MesBinam, L1)

2-Hydroxy-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-carbaldehyde (**SM8,** 254 mg, 0.999 mmol), (*R*)-[1,1'-binaphthalene]-2,2'-diamine (142 mg, 0.499 mmol) and methanol (8 ml) were mixed and then refluxed for 12 h. After allowing the reaction mixture to reach 22 °C, the resulting precipitate was isolated by filtration, washed with a small amount of cold methanol and then dried *in vacuo* at 70 °C to give **L1** (289 mg, 76%) as a powder of orange color. **MP** >200 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 11.91 (s, 2H), 8.26 (s, 2H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.41–7.33 (m, 4H), 7.24–7.17 (m, 4H), 6.93 (s, 2H), 6.89 (m, 4H), 6.72 (d, *J* = 2.2 Hz, 2H),

2.31 (s, 6H), 2.25 (s, 6H), 2.04 (s, 6H), 1.87 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 164.6, 155.8, 146.4, 136.8, 136.51, 136.45, 135.3, 134.2, 133.2, 132.3, 131.7, 130.2, 128.6, 128.4, 128.2, 128.1, 127.5, 127.0, 126.9, 126.8, 125.5, 119.1, 118.7, 21.2, 20.51, 20.46, 20.45. **IR** (neat, cm^{-1}): 2917, 1582, 1451, 1260, 1181, 1110, 820, 745. **HRMS** (ESI) *m/z* calculated for $C_{54}H_{49}N_2O_2^+$ ($M + H^+$) 757.3789, found 757.3783. **Specific rotation**: $[\alpha]^{22}_D$ = -172.5 (*c* = 0.97, $CHCl_3$).

(*R*)-MesBinamAlCl (**ML1**, (*R*)-MesBinam = (*R*)-3,3''-(([1,1'-binaphthalene]-2,2'-diyl-bis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-olate))

Et_2AlCl (Aldrich, 1.0 M, hexanes, 1.05 ml, 1.05 mmol) was added to a solution of (*R*)-3,3''-(([1,1'-binaphthalene]-2,2'-diylbis(azanylylidene))bis(methanylylidene))bis-(2',4',5,6'-tetramethyl-[1,1'-biphenyl]-2-ol) ((*R*)-MesBinam, **L1**, 724 mg, 0.957 mmol) in DCM (12 ml) at 0 °C. The resulting solution was stirred at 22 °C for 12 h, followed by removal of volatiles *in vacuo*. The residue was suspended in boiling cyclohexane, and filtered through celite while still hot. The filtrate was allowed to slowly reach 22 °C. The resulting precipitate was isolated by filtration, washed twice with pentane and subsequently dried *in vacuo* at 80 °C to give (*R*)-MesBinamAlCl (**ML1**, 394 mg, 50%) as a bright yellow solid. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$, -55 °C): δ 8.40 (s, 1H), 8.25 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.51 (dt, *J* = 9.9, 7.2 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 1H), 7.32–7.26 (m, 2H), 7.14 (d, *J* = 8.5 Hz, 1H), 7.10 (s, 1H), 7.08–7.03 (m, 3H), 6.98 (s, 1H), 6.96 (s, 1H), 6.92 (s, 1H), 6.86 (s, 1H), 6.79 (s, 1H), 2.47 (s, 3H), 2.39 (s,

3H), 2.19 (s, 3H), 2.15 (s, 3H), 2.06 (s, 3H), 1.93 (s, 3H), 1.89 (s, 3H), 1.65 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$, -55 °C): δ 174.0, 169.1, 163.3, 159.3, 144.2, 143.9, 141.1, 139.9, 138.9, 137.6, 136.9, 135.8, 135.7, 135.2, 135.1, 133.9, 133.7, 132.7, 132.5, 132.4, 132.3, 132.2, 131.91, 131.90, 129.99, 129.47, 128.5, 128.2, 127.9, 127.8, 127.75, 127.6, 127.03, 126.97, 126.85, 126.5, 126.3, 126.23, 126.22, 126.19, 126.0, 125.8, 125.5, 125.2, 119.0, 118.6, 21.7, 21.44, 21.35, 21.27, 20.5, 20.41, 20.36, 19.15. **IR** (neat, cm^{-1}): 2916, 1551, 1456, 1218, 977, 821, 749. **HRMS** (ESI) *m/z* calculated for $C_{54}H_{46}AlN_2O_2^+$ $(M - Cl)^+$ 781.3369, found 781.3375.

Note: NMR spectra collected in $CDCl_3$ at 22 °C displayed very broad resonances.

[(*R*)-MesBinamAl]$^+$[Co(CO)$_4$]$^-$ ((*R*)-**6b**, (*R*)-MesBinam = (*R*)-3,3''-(([1,1'-binaphthalene]-2,2'-diylbis(azanylylidene))bis(methanylylidene))bis(2',4',5,6'-tetra-methyl-[1,1'-biphenyl]-2-olate))

$NaCo(CO)_4$ (17.8 mg, 91.8 μmol), (*R*)-MesBinamAlCl (**ML1**, 75.0 mg, 91.8 μmol) and THF (4 ml) were mixed and stirred for 12 h at 22 °C. The reaction mixture was filtered through a 0.45 μm teflon syringe filter, carefully layered with hexane and then placed in a freezer at -34 °C for two days to give brown crystals of (*R*)-**6b**. A yield could not be obtained due to the unknown solvation state of (*R*)-**6b** upon isolation and drying *in vacuo*. **^{1}H NMR** (300 MHz, C_6D_6 + THF-d_8): δ 8.00 (s, 4H), 7.64 (d, *J* = 8.0 Hz, 4H), 7.12–7.02 (m, 6H), 6.96–6.91 (m, 2H), 6.88 (s, 2H), 6.66 (s, 2H), 6.53 (s, 2H), 2.29 (s, 6H), 1.92 (s, 6H), 1.86 (s, 6H), 1.79 (s, 6H). **^{13}C NMR** (126 MHz, THF-d_8): δ 173.2, 161.5, 146.8, 141.0, 138.8, 137.5, 135.9, 135.7, 134.2, 133.4, 133.3, 132.9, 131.6, 129.5, 129.2, 128.8, 128.0, 127.7, 127.5, 127.4, 126.9, 123.3,

120.7, 22.4, 21.2, 20.4, 20.3. **IR** (neat, cm^{-1}): 2916, 1878 $\nu_{(C=O)}$, 1616, 1588, 1551, 1440, 1218, 822.

Neither MS nor elemental analysis could be obtained to a satisfactory degree due to the unknown solvation state of (*R*)-**6b** in isolated form.

(*R*)-5',5''''-((1*E*,1'*E*)-([1,1'-Binaphthalene]-2,2'-diylbis(azanylylidene))-bis(methanylylidene))bis(2,2'',6,6''tetramethyl-[1,1':3',1''-terphenyl]-4'-ol) ((*R*)-Xyl$_2$Binam, L2)

4'-Hydroxy-2,2'',6,6''-tetramethyl-[1,1':3',1''-terphenyl]-5'-carbaldehyde (**SM10**, 662 mg, 2.00 mmol), (*R*)-[1,1'-binaphthalene]-2,2'-diamine (285 mg, 1.00 mmol) and ethanol (14 ml) were mixed and then refluxed for 12 h. After allowing the reaction mixture to reach 22 °C, the resulting precipitate was isolated by filtration, washed with ethanol, then pentane, and then dried *in vacuo* at 70 °C. The obtained powder was dissolved in DCM, layered with hexane, and left standing open to the atmosphere until most of the solvent had evaporated. The resulting precipitate was isolated by filtration, washed with pentane, and then dried *in vacuo* at 70 °C to give **L2** (596 mg, 66%) as a powder of orange color. **MP** 177 °C (decomp.). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.25 (s, 2H), 8.45 (s, 2H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.40 (dt, *J* = 8.1, 3.9 Hz, 2H), 7.25 (d, *J* = 3.4 Hz, 4H), 7.16 (t, *J* = 7.4 Hz, 2H), 7.11–7.05 (m, 6H), 7.00 (t, *J* = 7.8 Hz, 4H), 6.87 (d, *J* = 2.1 Hz, 2H), 6.82 (d, *J* = 2.1 Hz, 2H), 2.03 (s, 6H), 1.96 (s, 6H), 1.93 (s, 6H), 1.89 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ 163.7, 156.8, 145.3, 140.7, 137.0, 136.7, 136.6, 136.5, 136.4, 135.4, 133.4, 132.4, 131.7, 131.3, 130.0, 129.0, 128.3, 127.7, 127.6, 127.4, 127.3, 127.2,

127.11, 127.10, 126.9, 126.7, 125.7, 119.2, 118.6, 21.1, 20.9, 20.46, 20.46. **IR** (neat, cm^{-1}): 2915, 1580, 1447, 1195, 971, 765, 744. **HRMS** (ESI) *m/z* calculated for $C_{66}H_{57}N_2O_2^+$ ($M + H^+$) 909.4415, found 909.4410. **Specific rotation**: $[\alpha]^{22}_D$ = -352.1 (*c* = 0.45, $CHCl_3$).

(*R*)-Xyl$_2$BinamAlCl (**ML2**, (*R*)-Xyl$_2$Binam = (*R*)-5',5''''-((1*E*,1'*E*)-([1,1'-binaphthalene]-2,2'-diylbis(azanylylidene))bis(methanylylidene))bis(2,2'',6,6''-tetramethyl-[1,1':3',1''-terphenyl]-4'-olate)

Et_2AlCl (Aldrich, hexanes, 1.0 M, 400 µl, 0.400 mmol) was added to a solution of (*R*)-5',5''''-((1*E*,1'*E*)-([1,1'-binaphthalene]-2,2'-diylbis(azanylylidene))bis(methanylylidene))bis(2,2'',6,6''tetramethyl-[1,1':3',1''-terphenyl]-4'-ol) ((*R*)-Xyl$_2$Binam, **L2**, 327 mg, 0.360 mmol) in DCM (2 ml) at 0 °C. The reaction mixture was stirred at 22 °C for 12 h, and the resulting precipitate was isolated by filtration, washed with a small amount of DCM, and subsequently dried *in vacuo* at 80 °C to give (*R*)-Xyl$_2$BinamAlCl (**ML2**, 172 mg, 49%) as a bright yellow solid. **MP** >200 °C. **^{1}H NMR** (500 MHz, $CDCl_3$, -55 °C): δ 8.49 (s, 1H), 8.29 (s, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 8.06–8.01 (m, 3H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.58–7.52 (m, 3H), 7.37–7.28 (m, 4H), 7.20–7.03 (m, 14H), 6.99 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 2.13 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 2.00 (s, 3H), 1.97 (s, 3H), 1.72 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 174.9, 169.5, 163.9, 160.1, 144.3, 144.2, 140.56, 140.56, 140.27, 140.25, 139.5, 139.1, 137.9, 137.6, 136.9, 136.79, 136.78, 136.7, 136.4, 135.7, 134.1, 133.31, 133.31, 133.17, 133.17, 132.64, 132.63, 132.3, 132.1, 132.03, 132.00, 130.3, 129.9, 129.8, 129.1, 128.6, 127.9, 127.5, 127.3, 127.23,

127.17, 127.08, 127.05, 126.97, 126.95, 126.94, 126.86, 126.8, 126.53, 126.53, 126.4, 126.24, 126.19, 126.07, 126.07, 125.3, 119.4, 119.1, 21.74, 21.69, 21.5, 21.33, 21.25, 21.2, 20.8, 19.1. **IR** (neat, cm^{-1}): 2917, 1543, 1439, 1279, 1192, 1137, 881, 769, 746. **HRMS** (ESI) *m/z* calculated for $C_{66}H_{54}AlN_2O_2^+$ $(M - Cl)^+$ 933.3995, found 933.4019. *Note*: NMR spectra collected in $CDCl_3$ at 22 °C displayed very broad resonances.

3.5.2.4 Carbonylative Desymmetrization of Meso Epoxides Using Catalyst (R)-6b

(3*R*,4*R*)-3,4-Dimethyloxetan-2-one (5b)

General procedure B was followed using (*R*)-**ML1** (0.025 M, THF, 400 μl, 0.010 mmol, 2.5 mol %), $NaCo(CO)_4$ (0.0250 M, THF, 400 μl, 0.010 mmol, 2.5 mol %) and *meso* (2*R*,3*S*)-2,3-dimethyloxirane (28.7 mg, 0.398 mmol). The reaction mixture was stirred for 24 h at 22 °C. The volatility of **5b** interfered with its quantitative isolation, thus the yield of the reaction was determined using the method of standard addition. To this end, the crude reaction mixture was filtered through a short plug of silica gel using THF as eluent. The eluate was placed in a volumetric flask and diluted with THF to a total volume of 5 ml. A 0.5 ml aliquot of this solution was then analyzed *via* GC analysis. Additional 0.5 ml aliquots from this stock solution were subsequently treated with increasing amounts of independently isolated **5b**, and the resulting mixtures also analyzed *via* GC analysis. The observed increase in signal for **5b** was then used to determine tha the yield of **5b** was approximately 37.8 mg (95%).

Analytical data for **5b** has previously been reported.[14c] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.35 (qd, J = 6.1, 4.0 Hz, 1H), 3.22 (qd, J = 7.5, 4.0 Hz, 1H), 1.56 (d, J =

6.3 Hz, 3H), 1.39 (d, J = 7.7 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.9, 76.2, 52.3, 20.1, 12.4. **Specific rotation**: $[\alpha]^{22}_D$ = +43.7 (c = 0.22, CHCl3).

The enantiomeric ratio (er) was determined to be 91.5 : 8.5 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **5b**:

The stereochemical identity of **5b** was determined by two methods. First, the specific rotation of **5b** was compared under identical conditions to that reported in the literature for (3*S*,4*S*)-3,4-dimethyloxetan-2-one[14c] and found to be of the opposite sign. Second, a *racemic* mixture of *trans*-3,4-dimethyloxetan-2-one was kinetically resolved to enantiopure (3*R*,4*R*)-3,4-dimethyloxetan-2-one by adapting a published procedure[51] using Lipase PS and benzyl alcohol. The β-lactone isolated from this reaction was identical with **5b** with regard to the sign of its specific rotation and its GC retention time.

(3*R*,4*R*)-3,4-Diethyloxetan-2-one (5c)

General procedure B was followed using (*R*)-**ML1** (8.2 mg, 0.010 mmol, 3.9 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 μl, 0.0100 mmol, 3.91 mol %) and *meso* (2*R*,3*S*)-2,3-diethyloxirane[37] (1.28 M, THF, 200 μl, 0.256 mmol). After stirring at 22 °C for 24 h, the crude reaction mixture was subjected to bulb-to-bulb distillation to give **5c** (23.0 mg, 70%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.17 (td, J = 6.6, 3.9 Hz, 1H), 3.12 (ddd, J = 8.5, 6.5, 4.0 Hz, 1H), 1.93–1.69 (m, 4H), 1.02 (t, J = 7.5 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.5, 78.8, 57.2,

27.6, 21.2, 11.4, 9.2. **IR** (neat, cm^{-1}): 2969, 2939, 2880, 1812, 1461, 1386, 1120, 1062, 954. **HRMS** (ESI) *m/z* calculated for $C_7H_{13}O_2^+$ ($M + H^+$) 129.0916, found 129.0922. **Specific rotation**: $[\alpha]^{22}_D = +19.9$ (*c* = 0.26, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 97.8 : 2.2 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **5c**:

The stereochemical identity of **5c** was determined by comparing the order of elution of the two enantiomers during GC analysis with that of **5b** and **5a**.

(3*R*,4*R*)-3,4-Dipropyloxetan-2-one (5a)

Using (*R*)-**6b**:

General procedure B was followed using (*R*)-**ML1** (14.3 mg, 0.0175 mmol, 7.00 mol %), $NaCo(CO)_4$ (0.100 M, THF, 175 µl, 0.018 mmol, 7.0 mol %) and *meso* (2*R*,3*S*)-2,3-dipropyloxirane[38] (1.00 M, THF, 250 µl, 0.250 mmol). After stirring at 22 °C for 24 h, the crude reaction mixture was subjected to bulb-to-bulb distillation to give **5a** (30.1 mg, 77%) as a yellow oil. Analytical data for **5a** has previously been reported.[50] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.22 (ddd, *J* = 7.4, 5.9, 4.0 Hz, 1H), 3.17 (ddd, *J* = 8.8, 6.6, 4.0 Hz, 1H), 1.88–1.77 (m, 2H), 1.75–1.64 (m, 2H), 1.51–1.37 (m, 4H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.7, 78.1, 56.1, 36.6, 30.1, 20.4, 18.5, 13.86, 13.86. **Specific rotation**: $[\alpha]^{22}_D$ = +19.1 (*c* = 0.77, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 96.9 : 3.1 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Using (*R*)-**6c**:

General procedure B was followed using (*R*)-**ML2** (9.7 mg, 0.0100 mmol, 10 mol %), $NaCo(CO)_4$ (1.00 M, THF, 100 μl, 0.0100 mmol, 10.0 mol %) and *meso* (2*R*,3*S*)-2,3-dipropyloxirane[38] (1.00 M, THF, 100 μl, 0.100 mmol). After stirring at 22 °C for 24 h, the crude reaction mixture was subjected to bulb-to-bulb distillation to give **5a** (11.9 mg, 76%) as a yellow oil.

The enantiomeric ratio (er) was determined to be 98.6 : 1.4 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **5a**:

The stereochemical identity of **5a** was determined by comparing the specific rotation of **5a** under identical conditions to that reported in the literature for (3*R*,4*R*)-3,4-dipropyloxetan-2-one.[50] The literature known compound and **5a** displayed the same sign of rotation.

(3*R*,4*R*)-3,4-Dibutyloxetan-2-one (5d)

General procedure B was followed using (*R*)-**ML1** (13.1 mg, 0.0160 mmol, 8.04 mol %), $NaCo(CO)_4$ (0.0800 M, THF, 200 μl, 0.016 mmol, 8.0 mol %) and *meso* (2*R*,3*S*)-2,3-dibutyloxirane[7] (0.994 M, THF, 200 μl, 0.199 mmol). After stirring at 22 °C for 24 h, the crude reaction mixture was subjected to bulb-to-bulb distillation to give **5d** (26.7 mg, 72%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.20 (ddd, *J* =

7.4, 6.0, 4.0 Hz, 1H), 3.15 (ddd, J = 8.7, 6.6, 3.9 Hz, 1H), 1.89–1.65 (m, 4H), 1.44–1.29 (m, 8H), 0.91 (t, J = 7.0 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.8, 78.3, 56.2, 34.2, 29.2, 27.7, 27.2, 22.50, 22.46, 14.0, 13.9. **IR** (neat, cm^{-1}): 2957, 2931, 2861, 1817, 1466, 1125, 1064, 838. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{21}O_2^+$ ($M + H^+$) 185.1542, found 185.1543. **Specific rotation**: $[\alpha]^{22}_D$ = +21.1 (c = 0.32, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 95.9 : 4.1 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **5d**:

The stereochemical identity of **5d** was determined by comparing the order of elution of the two enantiomers during GC analysis with that of **5b** and **5a**.

(3*R*,4*R*)-3,4-Bis(3-(2,2,2-trifluoroethoxy)propyl)oxetan-2-one (5e)

General procedure B was followed using (*R*)-**ML1** (25.5 mg, 0.0312 mmol, 12.5 mol %), $NaCo(CO)_4$ (0.0624 M, THF, 500 µl, 0.0312 mmol, 12.5 mol %) and *meso* 2,3-bis(3-(2,2,2-trifluoroethoxy)propyl)oxirane (**SM2**, 80.4 mg, 0.248 mmol). After stirring at 33 °C for 24 h, the crude reaction mixture was subjected to flash column chromatography to give **5e** (68.6 mg, 79%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.29 (td, J = 6.6, 4.1 Hz, 1H), 3.81 (qd, J = 8.7, 2.5 Hz, 4H), 3.70–3.60 (m, 4H), 3.25 (td, J = 7.6, 4.0 Hz, 1H), 1.98–1.65 (m, 8H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.1, 124.0 (q, J = 279.6 Hz), 77.7, 72.02, 71.95, 68.45 (q, J = 34.0 Hz), 68.44 (q, J = 34.0 Hz), 55.9, 31.2, 27.0, 25.4, 24.7. *Note*: The two CF_3-groups are

pseudohomotopic, thus only one signal was observed. **^{19}F NMR** (376 MHz, $CDCl_3$): δ -74.3 (td, *J* = 8.9, 2.6 Hz). **IR** (neat, cm^{-1}): 2923, 2853, 1816, 1445, 1275, 1121, 966, 826. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{19}F_6O_4^+$ ($M + H^+$) 353.1182, found 353.1197. **Specific rotation**: $[\alpha]^{22}_D$ = +21.2 (*c* = 0.32, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 92.0 : 8.0 by GC analysis (b-Dex225 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **5e**:

The stereochemical identity of **5e** was determined by comparing the order of elution of the two enantiomers during GC analysis with that of **5b** and **5a**.

3.5.2.5 Regiodivergent Carbonylation of cis-Epoxides Using Catalyst (R)-6b

(2*R*,3*R*)-Methyl 3-hydroxy-2-methylpentanoate (10b)

General procedure B was followed using (*R*)-**ML1** (8.3 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.00 mol %) and *rac*-(2*S*,3*R*)-2-ethyl-3-methyloxirane (*rac*-**7b**, 0.998 M, THF, 200 µl, 0.200 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **10b** (11.1 mg, 38%) as a yellow oil. Analytical data for this compound has previously been reported.[52] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.59 (dtd, *J* = 8.5, 6.5, 3.9 Hz, 1H), 2.56 (d, *J* = 6.7 Hz, 1H), 2.55 (td, *J* = 7.2, 6.5 Hz, 1H), 1.54 (dtt, *J* = 14.1, 7.5, 4.0 Hz, 1H), 1.47–1.36 (m, 1H), 1.21 (d, *J* = 7.2 Hz,

3H), 0.98 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.6, 74.8, 51.83, 44.9, 27.7, 14.4, 9.9. **Specific rotation**: $[\alpha]^{22}_D$ = -3.7 (c = 0.17, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 2.7 : 97.3 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material. Prior to GC analysis, ester **10b** was derivatized following general procedure C.

Stereochemical assignment of **10b**:

The stereochemical identity of **10b** was determined by comparing the specific rotation of **10b** under identical conditions to that reported in the literature for (2*R*,3*R*)-methyl 3-hydroxy-2-methylpentanoate.[52] The literature known compound and **10b** displayed the same sign of rotation.

(2*R*,3*R*)-Methyl 3-hydroxy-2-methylhexanoate (10c)

General procedure B was followed using (*R*)-**ML1** (8.4 mg, 0.010 mmol, 5.1 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.08 mol %) and *rac*-(2*R*,3*S*)-2-methyl-3-propyloxirane (*rac*-**7c**, THF, 0.983 M, 200 µl, 0.197 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **10c** (10.1 mg, 32%) as a yellow oil. Analytical data for this compound has previously been reported.[53] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.69–3.65 (m, 1H), 2.56–2.49 (m, 1H), 2.48 (broad s, 1H), 1.56–1.36 (m, 4H), 1.21 (d, J = 7.2 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ

176.6, 73.3, 51.9, 45.4, 37.1, 18.9, 14.5, 14.2. **Specific rotation**: $[\alpha]^{22}_{D}$ = -3.4 (*c* = 1.6, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 2.9 : 97.1 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material. Prior to GC analysis, ester **10c** was derivatized following general procedure C.

Stereochemical assignment of **10c**:

The stereochemical identity of **10c** was determined by comparing the specific rotation of **10c** under identical conditions to that reported in the literature for (2*R*,3*R*)-methyl 3-hydroxy-2-methylhexanoate.[53] The literature known compound and **10c** displayed the same sign of rotation.

(3*R*,4*R*)-3-Ethyl-4-propyloxetan-2-one (8f) and (3*R*,4*R*)-4-ethyl-3-propyloxetan-2-one (9f)

General procedure B was followed using (*R*)-**ML1** (8.4 mg, 0.010 mmol, 5.1 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.08 mol %) and *rac*-(2*R*,3*S*)-2-ethyl-3-propyloxirane[42] (*rac*-**7f**, 0.985 M, THF, 200 µl, 0.197 mmol). After stirring at 22 °C for 18.5 h, the crude reaction mixture was subjected to bulb-to-bulb distillation to give a mixture of **8f** and **9f** (17.0 mg, 61%) as a yellow oil. Analytical data for **8f**[54] and **9f**[50] has previously been reported. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.22 (ddd, *J* = 7.3, 6.1, 4.0 Hz, 1H, **8f**), 4.15 (td, *J* = 6.6, 4.0 Hz, 1H, **9f**), 3.20–3.09 (m, 2), 1.94–1.62 (m, 8H), 1.51–1.35 (m, 4H), 1.01 (t, *J* = 7.6 Hz, 3H, **8f**), 0.99 (t, *J* = 7.5 Hz, 3H, **9f**), 0.96 (t, *J* = 7.7 Hz, 3H, **8f**), 0.93 (t, *J* = 7.4 Hz, 3H, **9f**). **^{13}C NMR** (75

MHz, $CDCl_3$): δ 171.7 (**8f**), 171.6 (**9f**), 79.3 (**9f**), 77.5 (**8f**), 57.6 (**8f**), 55.6 (**9f**), 36.6 (**8f**), 30.0 (**9f**), 27.6 (**9f**), 21.1 (**8f**), 20.4 (**9f**), 18.5 (**8f**), 13.83 (**8f**), 13.83 (**9f**), 11.3 (**8f**), 9.2 (**9f**). **IR** (neat, cm^{-1}): 2964, 2936, 2877, 1814, 1463, 1383, 1124, 868, 821. **HRMS** (ESI) *m/z* calculated for $C_8H_{15}O_2^+$ ($M + H^+$) 143.1067, found 143.1074. **Specific rotation**: $[\alpha]^{22}_D = +11.6$ (*c* = 0.26, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 98.0 : 2.0 for **8f**, and 96.5 : 3.5 for **9f** by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **8f** and **9f**:

The stereochemical identity of **8f** and **9f** was determined by first identifying the main component in the corresponding *racemic* β-lactone mixture as *racemic* **9f** based on previously reported data.[50,54] As is explained for the carbonylation of *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane (**7a**, *vide infra*), (*R*)-**6b** preferentially forms (3*R*,4*R*)-4-alkyl-3-methyloxetan-2-one (**8**) and (3*R*,4*R*)-3-alkyl-4-methyloxetan-2-one (**9**). Assuming that this preference is not altered by substituting the methyl-group with an ethyl-group, and given that the elution profile of **8f** and **9f** in the GC trace resembles those of **8a-i** and **9a-e** (i.e. the major enantiomer elutes first for both regiosiomers), the major enantiomers of the two regioisomers should be (3*R*,4*R*)-3-ethyl-4-propyloxetan-2-one (**8f**) and (3*R*,4*R*)-4-ethyl-3-propyloxetan-2-one (**9f**). The sign of the specific rotation further supports this assignment, because it is identical to that of the mixtures of **8** and **9 a-e**.

(2*R*,3*R*)-Methyl 3-hydroxy-2-methylheptanoate (10a)

General procedure B was followed using (*R*)-**ML1** (8.2 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.00 mol %) and *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane[41] (*rac*-**7a**, 1.00 M, THF, 200 µl, 0.200 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **10a** (12.5 mg, 36%) as a yellow oil. Analytical data for this compound has previously been reported.[55] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.65 (ddd, *J* = 8.4, 6.3, 3.0 Hz, 1H), 2.56–2.49 (m, 1H), 2.49 (broad s, 1H). 1.52–1.25 (m, 6H), 1.21 (d, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.6, 73.5, 51.9, 45.3, 34.6, 27.8, 22.8, 14.5, 14.2. **Specific rotation**: $[\alpha]^{22}_D$ = -2.7 (*c* = 0.19, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 2.7 : 97.3 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material. Prior to GC analysis, ester **10a** was derivatized following general procedure C.

Stereochemical assignment of **10a**:

The stereochemical identity of **10a** was determined by comparing the specific rotation of **10a** under identical conditions to that reported in the literature for (2*R*,3*R*)-methyl 3-hydroxy-2-methylheptanoate.[55] The literature known compound and **10a** displayed the same sign of rotation.

(3*R*,4*R*)-4-Butyl-3-ethyloxetan-2-one (8g) and (3*R*,4*R*)-3-butyl-4-ethyloxetan-2-one (9g)

General procedure B was followed using (*R*)-**ML1** (8.4 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 μl, 0.0100 mmol, 5.00 mol %) and *rac*-(2*R*,3*S*)-2-butyl-3-ethyloxirane43 (*rac*-**7g**, 1.00 M, THF, 200 μl, 0.200 mmol). After stirring at 22 °C for 18.5 h, the crude reaction mixture was subjected to bulb-to-bulb distillation to give a mixture of **8g** and **9g** (22.8 mg, 73%) as a yellow oil. Analytical data for *racemic* **8g** has previously been reported.[56] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.22–4.17 (m, 1H, **8g**), 4.17–4.11 (m, 1H, **9g**), 3.17–3.07 (m, 2H), 1.92–1.62 (m, 8H), 1.44–1.26 (m, 8H), 1.00 (t, *J* = 7.4 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 3H), 0.90–0.86 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 171.6 (**8g**), 171.5 (**9g**), 79.2 (**9g**), 77.7 (**8g**), 57.5 (**8g**), 55.7 (**9g**), 34.2 (**8g**), 29.2 (**9g**), 27.6 (**9g**), 27.5 (**9g**), 27.1 (**8g**), 22.41 (**8g**), 22.38 (**9g**), 21.1 (**8g**), 13.9 (**8g**), 13.8 (**9g**), 11.3 (**8g**), 9.1 (**9g**). **IR** (neat, cm^{-1}): 2960, 2993, 2863, 1816, 1462, 1382, 1123, 851. **HRMS** (ESI) *m/z* calculated for $C_9H_{17}O_2^+$ ($M + H^+$) 157.1223, found 157.1233. **Specific rotation**: $[\alpha]^{22}_D$ = +5.2 (*c* = 0.35, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 98.6 : 1.4 for **8g**, and 95.0 : 5.0 for **9g** by GC analysis (b-Dex225 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **8g** and **9g**:

The stereochemical identity of **8g** and **9g** was determined by first identifying the main component in the corresponding *racemic* β-lactone mixture as *racemic* **9g** based

on previously reported data.[56] The identity of **8g** and **9g** was then further assigned based on the assignment made for **8f** and **9f**.

(2*R*,3*R*)-Methyl 3-hydroxy-2-methyloctanoate (10d)

General procedure B was followed using (*R*)-**ML1** (8.4 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.00 mol %) and *rac*-(2*R*,3*S*)-2-methyl-3-pentyloxirane (*rac*-**7d**, 1.00 M, THF, 200 µl, 0.200 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **10d** (12.9 mg, 34%) as a yellow oil. Analytical data for this compound has previously been reported.[57] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.66 (dt, *J* = 6.6, 4.1 Hz, 1H), 2.57–2.50 (m, 1H), 2.48 (broad s, 1H), 1.52–1.25 (m, 8H), 1.22 (d, *J* = 7.2 Hz, 3H), 0.91–0.87 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.6, 73.5, 51.8, 45.3, 34.8, 31.9, 25.3, 22.7, 14.5, 14.2. **Specific rotation**: $[\alpha]^{22}_D$ = -6.1 (*c* = 0.20, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 2.8 : 97.2 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material. Prior to GC analysis, ester **10d** was derivatized following general procedure C.

Stereochemical assignment of **10d**:

The stereochemical identity of **10d** was determined by comparing the specific rotation of **10d** under identical conditions to that reported in the literature for (2*R*,3*R*)-

methyl 3-hydroxy-2-methyloctanoate.[57] The literature known compound and **10d** displayed the same sign of rotation.

(2*R*,3*R*)-Methyl 3-hydroxy-2-methylnonanoate (10e)

General procedure B was followed using (*R*)-**ML1** (8.4 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.00 mol %) and *rac*-(2*R*,3*S*)-2-hexyl-3-methyloxirane (*rac*-**7e**, 0.991 M, THF, 200 µl, 0.198 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **10e** (13.3 mg, 33%) as a yellow oil. Analytical data for this compound has previously been reported.[58] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.71 (s, 3H), 3.65 (td, *J* = 7.2, 6.1, 2.8 Hz, 1H), 2.57–2.49 (m, 1H), 2.48 (broad s, 1H), 1.52–1.24 (m, 10H), 1.21 (d, *J* = 7.3 Hz, 3H), 0.90–0.86 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.7, 73.5, 51.9, 45.3, 34.9, 31.9, 29.4, 25.6, 22.8, 14.5, 14.2. **Specific rotation**: $[\alpha]^{22}_D$ = -1.5 (*c* = 0.20, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 2.5 : 97.5 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material. Prior to GC analysis, ester **10e** was derivatized following general procedure C.

Stereochemical assignment of **10e**:

The stereochemical identity of **10e** was determined by comparing the specific rotation of **10e** under identical conditions to that reported in the literature for (2*R*,3*R*)-

methyl 3-hydroxy-2-methylnonanoate.[58] The literature known compound and **10e** displayed the same sign of rotation.

(2*R*,3*R*)-Methyl 3-hydroxy-2,6-dimethylheptanoate (10h)

General procedure B was followed using (*R*)-**ML1** (8.3 mg, 0.010 mmol, 5.1 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.08 mol %) and *rac*-(2*S*,3*R*)-2-isopentyl-3-methyloxirane (*rac*-**7h**, 0.983 M, THF, 200 µl, 0.197 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **10h** (13.4 mg, 36%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.69 (s, 3H), 3.62 (ddd, *J* = 8.1, 6.3, 3.8 Hz, 1H), 2.53 (p, *J* = 7.0 Hz, 1H), 2.50 (broad s, 1H), 1.60–1.16 (m, 5H), 1.19 (d, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 2.7 Hz, 3H), 0.86 (d, *J* = 2.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.6, 73.7, 51.8, 45.2, 34.7, 32.7, 28.1, 22.8, 22.5, 14.5. **IR** (neat, cm^{-1}): 3458, 2953, 2870, 1720, 1460, 1196, 1169, 1025. **HRMS** (ESI) *m/z* calculated for $C_{10}H_{20}NaO_3^+$ ($M + Na^+$) 211.1305, found 211.1307. **Specific rotation**: $[\alpha]^{22}_D$ = -3.3 (*c* = 0.11, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 3.1 : 96.9 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material. Prior to GC analysis, ester **10h** was derivatized following general procedure C.

Stereochemical assignment of **10h**:

The stereochemical identity of **10h** was determined by comparing the order of elution of the two enantiomers during GC analysis with that of **10a-e**.

(2*R*,3*R*)-Methyl 6-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-methylhexanoate (10i)

General procedure B was followed using (*R*)-**ML1** (8.4 mg, 0.010 mmol, 5.1 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 μl, 0.0100 mmol, 5.05 mol %) and *rac-tert*-butyldimethyl(3-((2*S*,3*R*)-3-methyloxiran-2-yl)propoxy)silane (*rac*-**7i**, 0.991 M, THF, 200 μl, 0.198 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol), stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **10i** (20.0 mg, 35%) as a yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 3.73–3.63 (m, 1H), 3.69 (s, 3H), 3.65 (t, *J* = 5.8 Hz, 2H), 3.13 (broad s, 1H), 2.54 (p, *J* = 7.1 Hz, 1H), 1.71–1.60 (m, 3H), 1.52–1.39 (m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 176.4, 73.1, 63.3, 51.8, 45.5, 31.6, 29.0, 26.1, 18.4, 14.1, -5.2. **IR** (neat, cm^{-1}): 2952, 2857, 1739, 1462, 1254, 1093, 833, 774. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{31}O_4Si^+$ ($M + H^+$) 291.1986, found 291.1991. **Specific rotation**: $[\alpha]^{22}_D$ = -5.9 (*c* = 0.31, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 3.6 : 96.4 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material. Prior to GC analysis, ester **10i** was derivatized following general procedure C.

Stereochemical assignment of **10i**:

The stereochemical identity of **10i** was determined by comparing the order of elution of the two enantiomers during GC analysis with that of **10a-e**.

3.5.2.6 Regiodivergent Carbonylation of cis-Epoxides Using Catalyst (R)-6c

(3*S*,4*S*)-4-Ethyl-3-methyloxetan-2-one (*ent*-8b) and (3*S*,4*S*)-3-ethyl-4-methyl-oxetan-2-one (*ent*-9b)

General procedure B was followed using (*S*)-**6c** (9.8 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.00 mol %) and *rac*-(2*R*,3*S*)-2-ethyl-3-methyloxirane (*rac*-**7b**, 0.998 M, THF, 200 µl, 0.200 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to bulb-to-bulb distillation to give a mixture of *ent*-**8b** and *ent*-**9b** (15.1 mg, 66%) as a yellow oil. Analytical data for *ent*-**8b**[50] and *ent*-**9b**[14c] has previously been reported. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.41 (qd, *J* = 6.1, 4.0 Hz, 1H, *ent*-**9b**), 4.13 (td, *J* = 6.6, 4.0 Hz, 1H, *ent*-**8b**), 3.22 (qd, *J* = 7.5, 4.0 Hz, 1H, *ent*-**8b**), 3.13 (ddd, *J* = 8.4, 6.7, 4.0 Hz, 1H, *ent*-**9b**), 1.98–1.68 (m, 4H), 1.55 (d, *J* = 6.1 Hz, 3H, *ent*-**9b**), 1.39 (d, *J* = 7.5 Hz, 3H, *ent*-**8b**), 1.03 (t, *J* = 7.5 Hz, 3H, *ent*-**8b**), 1.00 (t, *J* = 7.6 Hz, 3H, *ent*-**9b**). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.1 (*ent*-**8b**), 171.2 (*ent*-**9b**), 80.6 (*ent*-**8b**), 74.2 (*ent*-**9b**), 59.0 (*ent*-**9b**), 50.4 (*ent*-**8b**), 27.3 (*ent*-**8b**), 21.0 (*ent*-**9b**), 20.4 (*ent*-**9b**), 12.7 (*ent*-**8b**), 11.2 (*ent*-**9b**), 9.1 (*ent*-**8b**). **Specific rotation**: $[\alpha]^{22}_D$ = -16.0 (*c* = 0.23, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 2.7 : 97.3 for *ent*-**8b**, and 4.5 : 95.5 for *ent*-**9b** by GC analysis (b-Dex225 column) in comparison to authentic *racemic* material.

Stereochemical assignment of *ent*-**8b** and *ent*-**9b**:

The stereochemical identity of *ent*-**8b** and *ent*-**9b** was determined by first identifying the main component in the corresponding *racemic* β-lactone mixture as *racemic* **8b** based on previously reported data.[14c,50] As is explained for the carbonylation of *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane (**7a**), (*R*)-**6b** preferentially forms (3*R*,4*R*)-4-alkyl-3-methyloxetan-2-one (**8**) and (3*R*,4*R*)-3-alkyl-4-methyloxetan-2-one (**9**). Consequently, (*S*)-**6b** should preferentially form (3*S*,4*S*)-4-ethyl-3-methyloxetan-2-one (*ent*-**8b**) and (3*S*,4*S*)-3-ethyl-4-methyloxetan-2-one (*ent*-**9b**).

(3*R*,4*R*)-3-Methyl-4-propyloxetan-2-one (8c) and (3*R*,4*R*)-4-methyl-3-propyloxetan-2-one (9c)

General procedure B was followed using (*R*)-**6c** (9.7 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 μl, 0.0100 mmol, 5.00 mol %) and *rac*-(2*R*,3*S*)-2-methyl-3-propyloxirane (*rac*-**7c**, 0.997 M, THF, 200 μl, 0.199 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to bulb-to-bulb distillation followed by flash column chromatography to give a mixture of **8c** and **9c** (19.0 mg, 74%) as a yellow oil. Analytical data for **8c**[50] and **9c**[51] has previously been reported. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.40 (qd, *J* = 6.1, 3.9 Hz, 1H, **9c**), 4.18 (ddd, *J* = 7.3, 6.2, 4.0 Hz, 1H, **8c**), 3.26–3.14 (m, 2H), 1.90–1.65 (m, 4H), 1.55 (d, *J* = 6.1 Hz, 3H, **9c**), 1.50–1.34 (m, 4H), 1.38 (d, *J* = 7.5 Hz, 3H, **8c**), 0.98 (t, *J* = 7.5 Hz, 3H, **8c**), 0.95 (t, *J* = 7.3 Hz, 3H, **9c**). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 172.2 (**8c**), 171.4 (**9c**), 79.5 (**8c**), 74.7 (**9c**), 57.5 (**9c**), 50.8 (**8c**), 36.2 (**8c**), 29.8 (**9c**), 20.4 (**9c**), 20.3 (**9c**), 18.5 (**8c**), 13.80 (**8c**), 13.79 (**9c**), 12.6 (**8c**). **Specific rotation**: $[\alpha]^{22}_D$ = +9.9 (*c* = 0.29, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 97.2 : 2.8 for **8c**, and 95.9 : 4.1 for **9c** by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **8c** and **9c**:

The stereochemical identity of **8c** and **9c** was determined by first identifying the main component in the corresponding *racemic* β-lactone mixture as *racemic* **8c** based on previously reported data.[50,51] As is explained for the carbonylation of *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane (**7a**), (*R*)-**6b** preferentially forms (3*R*,4*R*)-4-alkyl-3-methyloxetan-2-one (**8**) and (3*R*,4*R*)-3-alkyl-4-methyloxetan-2-one (**9**). Consequently, the major enantiomers of the two regioisomers should be (3*R*,4*R*)-3-methyl-4-propyloxetan-2-one (**8c**) and (3*R*,4*R*)-4-methyl-3-propyloxetan-2-one (**9c**).

(3*R*,4*R*)-3-Ethyl-4-propyloxetan-2-one (8f) and (3*R*,4*R*)-4-ethyl-3-propyloxetan-2-one (9f)

General procedure B was followed using (*R*)-**6c** (15.5 mg, 0.0160 mmol, 8.08 mol %), $NaCo(CO)_4$ (0.0800 M, THF, 200 µl, 0.0160 mmol, 8.08 mol %) and *rac*-(2*R*,3*S*)-2-ethyl-3-propyloxirane[10] (*rac*-**7f**, 0.992 M, THF, 200 µl, 0.198 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to bulb-to-bulb distillation followed by flash column chromatography to give a mixture of **8f** and **9f** (18.7 mg, 66%) as a yellow oil.

For analytical data and stereochemical assignment see the analogous reaction using catalyst (*R*)-**6b** in Section 3.5.2.5.

The enantiomeric ratio (er) was determined to be 99.2 : 0.8 for **8f**, and 98.4 : 1.6 for **9f** by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

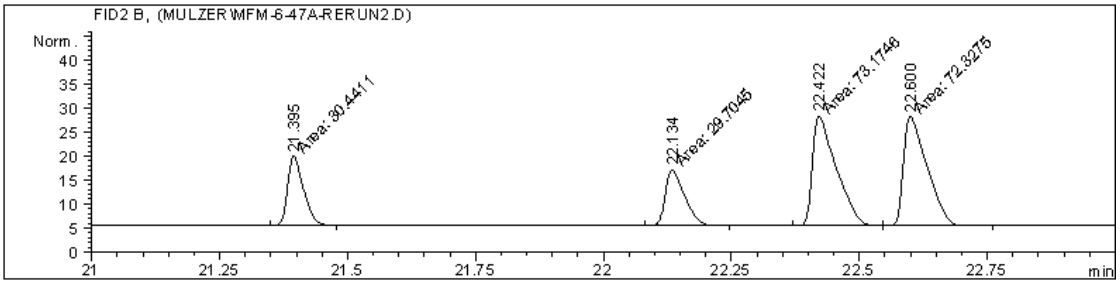
(3*R*,4*R*)-4-Butyl-3-methyloxetan-2-one (8a) and (3*R*,4*R*)-3-butyl-4-methyloxetan-2-one (9a)

General procedure B was followed using (*R*)-**6c** (9.7 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.00 mol %) and *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane[9] (*rac*-**7a**, 1.00 M, THF, 200 µl, 0.200 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to bulb-to-bulb distillation followed by flash column chromatography to give a mixture of **8a** and **9a** (20.9 mg, 73%) as a yellow oil. Analytical data for **8a**[50] has previously been reported. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.40 (qd, *J* = 6.1, 4.0 Hz, 1H, **9a**), 4.17 (td, *J* = 6.7, 4.0 Hz, 1H, **8a**), 3.26–3.13 (m, 2H), 1.92–1.66 (m, 4H), 1.56 (d, *J* = 6.2 Hz, 3H, **9a**), 1.48–1.31 (m, 8H), 1.38 (d, *J* = 7.5 Hz, 3H, **8a**), 0.95–0.89 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.2 (**8a**), 171.5 (**9a**), 79.7 (**8a**), 74.7 (**9a**), 57.6 (**9a**), 50.8 (**8a**), 33.9 (**8a**), 29.1 (**9a**), 27.5 (**9a**), 27.1 (**8a**), 22.43 (**9a**), 22.40 (**8a**), 20.4 (**9a**), 14.0 (**8a**), 13.9 (**9a**), 12.6 (**8a**). **IR** (neat, cm^{-1}): 2959, 2933, 2863, 1816, 1457, 1386, 1124, 828. **HRMS** (ES) *m/z* calculated for $C_8H_{14}O_2^+$ (M^+) 142.0994, found 142.0990. **Specific rotation**: $[\alpha]^{22}_D$ = +15.4 (*c* = 0.28, $CHCl_3$).

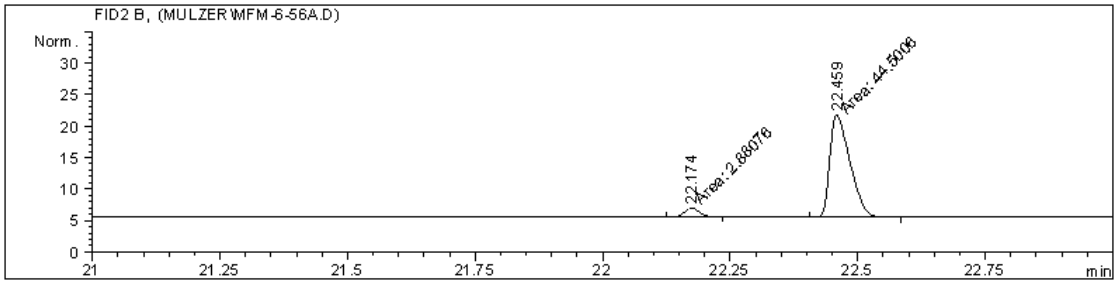
The enantiomeric ratio (er) was determined to be 95.1 : 4.9 for **8a**, and 95.6 : 4.4 for **9a** by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **8a** and **9a**:

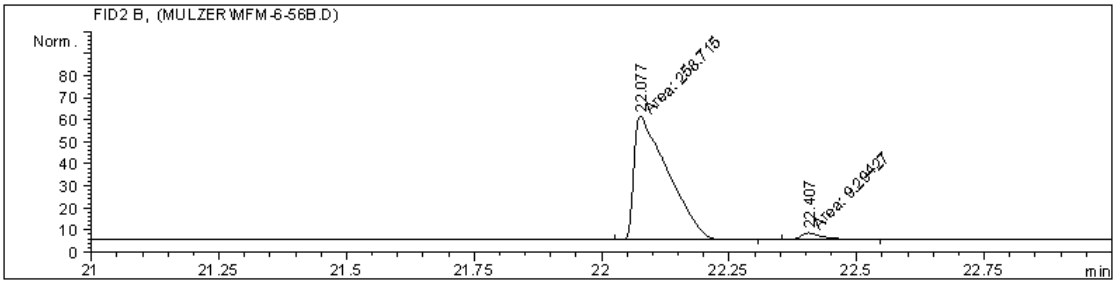
The stereochemical identity of **8a** and **9a** was determined using a combination of ^{1}H NMR and GC analysis. First, *rac*-(2*R*,3*S*)-2-butyl-3-methyloxirane was carbonylated using $[ClTPPAl(THF)_2]^+[Co(CO)_4]^-$ to give a corresponding *racemic* mixture of *rac*-**8a** and *rac*-**9a**. The major component in this β-lactone mixture was identified as *rac*-**8a** based on previously reported data.[50] Consequently, the two main peaks in the GC trace below (b-Dex225 column) can be attributed to *rac*-**8a**, whereas the two minor peaks stem from *rac*-**9a**.



Next, enantioenriched (2*R*,3*S*)-2-butyl-3-methyloxirane (**7a**) was carbonylated using (*R*)-**6c**, and the resulting β-lactone mixture analyzed by ^{1}H NMR and GC (cf. Scheme 3.4). The main component was (3*R*,4*R*)-4-butyl-3-methyloxetan-2-one (**8a**), which allowed for identification of the main peak in the corresponding GC trace as **8a**, and the minor peak as (3*S*,4*S*)-3-butyl-4-methyloxetan-2-one (*ent*-**9a**).



Carbonylation of enantioenriched **7a** using (*S*)-**6c** yielded *ent*-**9a** as the main product and **8a** as the minor component as can be seen in the following GC trace.



In analogy, carbonylation of (2*S*,3*R*)-2-butyl-3-methyloxirane (*ent*-**7a**) using (*R*)-**6c** should give (3*R*,4*R*)-3-butyl-4-methyloxetan-2-one (**9a**) as the major product and (3*S*,4*S*)-4-butyl-3-methyloxetan-2-one (*ent*-**8a**) as the minor product. Consequently, carbonylation of *racemic* **7a** using (*R*)-**6c** should yield (3*R*,4*R*)-4-butyl-3-methyloxetan-2-one (**8a**) and (3*R*,4*R*)-3-butyl-4-methyloxetan-2-one (**9a**) as the main products. Generally speaking, carbonylation of *racemic cis*-epoxides **7** using (*R*)-**6c** yields (3*R*,4*R*)-4-alkyl-3-methyloxetan-2-ones (**8**) and (3*R*,4*R*)-3-alkyl-4-methyloxetan-2-ones (**9**) as the main products, and (3*S*,4*S*)-4-alkyl-3-methyloxetan-2-ones (*ent*-**8**) and (3*S*,4*S*)-3-alkyl-4-methyloxetan-2-ones (*ent*-**9**) as the minor products.

(3*R*,4*R*)-4-Butyl-3-ethyloxetan-2-one (8g) and (3*R*,4*R*)-3-butyl-4-ethyloxetan-2-one (9g)

General procedure B was followed using (*R*)-**6c** (15.5 mg, 0.0160 mmol, 8.00 mol %), $NaCo(CO)_4$ (0.0800 M, THF, 200 µl, 0.0160 mmol, 8.00 mol %) and *rac*-(2*R*,3*S*)-2-butyl-3-ethyloxirane[43] (*rac*-**7g**, 1.00 M, THF, 200 µl, 0.200 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to bulb-to-bulb distillation

followed by flash column chromatography to give a mixture of **8g** and **9g** (21.0 mg, 67%) as a yellow oil.

For analytical data and stereochemical assignment see the analogous reaction using catalyst (*R*)-**6b** in Section 3.5.2.5.

The enantiomeric ratio (er) was determined to be 98.2 : 1.8 for **8g**, and 97.5 : 2.5 for **9g** by GC analysis (b-Dex225 column) in comparison to authentic *racemic* material.

(3*R*,4*R*)-3-Methyl-4-pentyloxetan-2-one (8d) and (3*R*,4*R*)-4-methyl-3-pentyl-oxetan-2-one (9d)

General procedure B was followed using (*R*)-**6c** (15.5 mg, 0.0160 mmol, 8.04 mol %), $NaCo(CO)_4$ (0.0800 M, THF, 200 µl, 0.0160 mmol, 8.04 mol %) and *rac*-(2*R*,3*S*)-2-methyl-3-pentyloxirane (*rac*-**7d**, 0.993 M, THF, 200 µl, 0.199 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to bulb-to-bulb distillation followed by flash column chromatography to give a mixture of **8d** and **9d** (22.2 mg, 71%) as a yellow oil. Analytical data for *racemic* **8d**[59] has previously been reported. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.40 (qd, *J* = 6.1, 3.9 Hz, 1H, **9d**), 4.17 (td, *J* = 6.7, 4.0 Hz, 1H, **8d**), 3.22 (qd, *J* = 7.6, 4.0 Hz, 1H, **8d**), 3.16 (ddd, *J* = 8.9, 6.5, 3.9 Hz, 1H, **9d**), 1.90–1.67 (m, 4H), 1.55 (d, *J* = 6.0 Hz, 3H), 1.49–1.25 (m, 12H), 1.38 (d, *J* = 7.5 Hz, 3H), 0.91–0.87 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.2 (**8d**), 171.5 (**9d**), 79.7 (**8d**), 74.8 (**9d**), 57.7 (**9d**), 50.8 (**8d**), 34.2 (**8d**), 31.50 (**9d**), 31.46 (**8d**), 27.7 (**9d**), 26.6 (**9d**), 24.7 (**8d**), 22.54 (**8d**), 22.46 (**9d**), 20.4 (**9d**), 14.04 (**9d**), 14.02 (**8d**), 12.6 (**8d**). **IR** (neat, cm^{-1}): 2931, 2860, 1817, 1458, 1125, 863, 830. **HRMS** (ESI) *m/z*

calculated for $C_9H_{17}O_2^+$ ($M + H^+$) 157.1223, found 157.1220. **Specific rotation**: $[\alpha]^{22}_D$ = +10.5 (*c* = 0.34, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 95.1 : 4.9 for **8d**, and 96.1 : 3.9 for **9d** by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **8d** and **9d**:

The stereochemical identity of **8d** and **9d** was assigned in analogy to the procedure used for **8c** and **9c**.

(3*R*,4*R*)-4-Hexyl-3-methyloxetan-2-one (8e) and (3*R*,4*R*)-3-hexyl-4-methyloxetan-2-one (9e)

General procedure B was followed using (*R*)-**6c** (9.7 mg, 0.010 mmol, 5.0 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.03 mol %) and *rac*-(2*R*,3*S*)-2-hexyl-3-methyloxirane (*rac*-**7e**, 0.994 M, THF, 200 µl, 0.199 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to bulb-to-bulb distillation followed by flash column chromatography to give a mixture of **8e** and **9e** (22.8 mg, 67%) as a yellow oil. Analytical data for *racemic* **8e**[60] has previously been reported. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.40 (qd, *J* = 6.1, 4.0 Hz, 1H, **9e**), 4.17 (td, *J* = 6.6, 3.9 Hz, 1H, **8e**), 3.26–3.13 (m, 2H), 1.92–1.66 (m. 4H), 1.55 (d, *J* = 6.1 Hz, 3H), 1.47–1.22 (m, 16H), 1.38 (d, *J* = 7.6 Hz, 3H), 0.90–0.86 (m, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$): δ 172.2 (**8e**), 171.5 (**9e**), 79.7 (**8e**), 74.7 (**9e**), 57.7 (**9e**), 50.8 (**8e**), 34.2 (**8e**), 31.7 (**8e**), 31.6 (**9e**), 29.00 (**9e**), 28.96 (**8e**), 27.8 (**9e**), 26.9 (**9e**), 25.0 (**8e**), 22.60 (**9e**),

22.57 (**8e**), 20.4 (**9e**), 14.11 (**9e**), 14.11 (**8e**), 12.6 (**8e**). **IR** (neat, cm^{-1}): 2929, 2858, 1819, 1458, 1124, 828. **HRMS** (EI) *m/z* calculated for $C_{10}H_{18}O_2^+$ (M^+) 170.1307, found 170.1311. **Specific rotation**: $[\alpha]^{22}_D = +12.4$ (*c* = 0.35, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 94.8 : 5.2 for **8e**, and 96.0 : 4.0 for **9e** by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **8e** and **9e**:

The stereochemical identity of **8e** and **9e** was assigned in analogy to the procedure used for **8c** and **9c**.

(3*R*,4*R*)-4-Isopentyl-3-methyloxetan-2-one (8h) and (3*R*,4*R*)-3-isopentyl-4-methyl-oxetan-2-one (9h)

General procedure B was followed using (*R*)-**6c** (9.7 mg, 0.010 mmol, 5.1 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.08 mol %) and *rac*-(2*S*,3*R*)-2-isopentyl-3-methyloxirane (*rac*-**7h**, 0.983M, THF, 200 µl, 0.197 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was subjected to bulb-to-bulb distillation followed by flash column chromatography to give a mixture of **8h** and **9h** (20.7 mg, 66%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.40 (qd, *J* = 6.1, 3.9 Hz, 1H, **9h**), 4.15 (td, *J* = 6.7, 4.0 Hz, 1H, **8h**), 3.21 (qd, *J* = 7.5, 4.0 Hz, 1H, **8h**), 3.14 (ddd, *J* = 8.9, 6.5, 3.9 Hz, 1H, **9h**), 1.91–1.67 (m, 4H), 1.62–1.51 (m, 2H), 1.55 (d, *J* = 6.2 Hz, 3H, **9h**), 1.38 (d, *J* = 7.5 Hz, 3H, **8h**), 1.36–1.28 (m, 2H), 1.27–1.16 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 6H, **9h**), 0.90 (d, *J* = 6.6 Hz, 6H, **8h**). **^{13}C NMR** (75 MHz,

$CDCl_3$): δ 172.2 (**8h**), 171.5 (**9h**), 79.9 (**8h**), 74.7 (**9h**), 57.8 (**9h**), 50.8 (**8h**), 35.9 (**9h**), 33.9 (**8h**), 32.2 (**8h**), 27.92 (**9h**), 27.86 (**8h**), 25.7 (**9h**), 22.51 (**8h**), 22.48 (**8h**), 22.45 (**9h**), 22.45 (**9h**), 20.47 (**9h**), 12.7 (**8h**). **IR** (neat, cm^{-1}): 2956, 2872, 1816, 1457, 1122, 829. **MS** (ESI) *m/z* calculated for $C_9H_{17}O_2^+$ ($M + H^+$) 157.1, found 157.1. **Specific rotation**: $[\alpha]^{22}_D = +10.0$ (*c* = 0.22, $CHCl_3$).

The enantiomeric ratio (er) was determined to be 91.6 : 8.4 for **8h**, and 95.4 : 4.6 for **9h** by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material.

Stereochemical assignment of **8h** and **9h**:

The stereochemical identity of **8h** and **9h** was assigned in analogy to the procedure used for **8c** and **9c**. Regioisomer **8h** was assumed to be the major regioisomer in the corresponding *racemic* β-lactone mixture in analogy to the observations made with **8a**-**e**.

(2*R*,3*R*)-Methyl 6-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-methylhexanoate (10i) and (*R*)-Methyl 5-((*tert*-butyldimethylsilyl)oxy)-2-((*R*)-1-hydroxyethyl)pentanoate (11)

General procedure B was followed using (*R*)-**6c** (9.7 mg, 0.010 mmol, 5.1 mol %), $NaCo(CO)_4$ (0.0500 M, THF, 200 µl, 0.0100 mmol, 5.05 mol %) and *rac-tert*-butyldimethyl(3-((2*S*,3*R*)-3-methyloxiran-2-yl)propoxy)silane (*rac*-**7i**, 0.991 M, THF, 200 µl, 0.198 mmol). After stirring at 22 °C for 20 h, the crude reaction mixture was treated with methanol (0.4 ml) and sodium methoxide (ca. 14.0 mg, ca. 0.259 mmol),

stirred for 5 minutes at 22 °C and then concentrated under reduced pressure. The residue was subjected to flash column chromatography to give **10i** (21.8 mg, 38%) and **11** (23.0 mg, 40%) as two separate yellow oils.

Analytical data and stereochemical assignment for **10i** was given before when using catalyst (*R*)-**6b** in Section 3.5.2.5.

The enantiomeric ratio (er) for **10i** was determined to be 4.6 : 95.4 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material. Prior to GC analysis, ester **10i** was derivatized following general procedure C.

Analytical data for **11**:

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.92 (h, *J* = 6.4 Hz, 1H), 3.72 (s, 3H), 3.60 (t, *J* = 6.2 Hz, 2H), 2.51 (d, *J* = 5.9 Hz, 1H), 2.40 (dt, *J* = 7.5, 6.4 Hz, 1H), 1.73–1.65 (m, 2H), 1.56–1.46 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 176.1, 68.6, 62.7, 52.6, 51.7, 30.5, 26.1, 25.9, 21.7, 18.4, -5.2. **IR** (neat, cm^{-1}): 3460, 2953, 2857, 1737, 1254, 1096, 833, 774. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{30}O_4NaSi^+$ (M + Na^+) 313.1806, found 313.1815. **Specific rotation**: $[\alpha]^{22}_D$ = -5.8 (*c* = 0.20, $CHCl_3$).

The enantiomeric ratio (er) for **11** was determined to be 96.9 : 3.1 by GC analysis (b-Dex120 column) in comparison to authentic *racemic* material. Prior to GC analysis, the TBS-protecting group was removed using two equivalents of *para*-toluenesulfonic acid monohydrate in THF at 60 °C for 2.5 hours to give the corresponding lactone, 3-(1-hydroxyethyl)tetrahydro-2*H*-pyran-2-one. (**^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.32 (t, *J* = 6.0 Hz, 2H), 4.07 (s, 1H), 4.04–3.92 (m, 1H), 2.40 (dt, *J* = 11.9, 8.0 Hz, 1H), 2.08

(dq, J = 13.8, 7.2 Hz, 1H), 1.99–1.69 (m, 2H), 1.59–1.48 (m, 1H), 1.24 (d, J = 6.5 Hz, 3H). **MS** (ESI) *m/z* calculated for $C_7H_{13}O_2^+$ ($M + H^+$) 145.1, found 145.1). This lactone was then derivatized following general procedure C and subjected to GC analysis.

Stereochemical assignment of **11**:

The stereochemical identity of **11** was assigned based on the observation that (*R*)-**6b** preferentially forms (3*R*,4*R*)-3-alkyl-4-methyloxetan-2-ones (**9**). Since (3*R*,4*R*)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-4-methyloxetan-2-one (**9i**) is the precursor to **13** and stereochemistry is preserved in the ring-opening reaction using sodium methoxide, the product should be (*R*)-methyl 5-((*tert*-butyldimethylsilyl)oxy)-2-((*R*)-1-hydroxyethyl)pentanoate (**11**).

(2*R*,3*R*)-3-Hydroxy-2-methylnonanoic acid (12)

(2*R*,3*R*)-Methyl 3-hydroxy-2-methylnonanoate (**10e**) was converted to **14** using a previously published method.[61] Ester **10e** (12 mg, 0.059 mmol) was dissolved in a mixture of THF, methanol and water (1:1:1, 0.9 ml), and lithium hydroxide monohydrate (13 mg, 0.31 mmol) was added. The mixture was stirred at 22 °C until no more starting material was detected by TLC. Water was added and the reaction mixture extracted with DCM once. The aqueous phase was acidified using hydrochloric acid (1 M, aq.), and then extracted with Et_2O (3x). The organic phase was dried with sodium sulfate and subsequently concentrated under reduced pressure to give **12** as a colorless oil (10 mg, 90%). The analytical data matched that reported in

the literature.[61] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.68 (broad s, 1H), 3.70 (m, 1H), 2.56 (p, *J* = 7.1 Hz, 1H), 1.71–1.11 (m, 11H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.96–0.81 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 181.2, 73.5, 45.4, 34.7, 31.9, 29.3, 25.5, 22.8, 14.4, 14.2.

3.5.2.7 Crystallographic Data for Catalyst (R)-6b

Table 3.6 Crystal data and structure refinement for catalyst (*R*)-6b

Identification code	(*R*)-**6b**
Empirical formula	$C_{78}H_{86}AlCoN_2O_{11}$
Formula weight	1313.40
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P2(1)2(1)2(1)
Unit cell dimensions	a = 11.5495(11) Å α = 90°
	b = 21.268(2) Å β = 90°
	c = 28.170(3) Å γ = 90°
Volume	6919.5(12) $Å^3$
Z	4
Density (calculated)	1.261 Mg/m^3
Absorption coefficient	0.323 mm^{-1}
F(000)	2784
Crystal size	0.35 x 0.20 x 0.15 mm^3
Theta range for data collection	1.45 to 23.26°
Index ranges	-7<=h<=12, -19<=k<=23, -29<=l<=31
Reflections collected	21630
Independent reflections	9927 [R(int) = 0.0435]
Completeness to theta = 23.26°	99.9%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9532 and 0.8954
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9927 / 12 / 843
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0677, wR2 = 0.1659
R indices (all data)	R1 = 0.0988, wR2 = 0.1836
Absolute structure parameter	0.00(3)
Largest diff. peak and hole	0.301 and -0.415 e.$Å^{-3}$

Table 3.7 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for catalyst (*R*)-6b

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
Al(1)	724(1)	5441(1)	-2037(1)	30(1)
O(1)	148(3)	5973(2)	-2481(1)	32(1)
O(2)	1485(3)	4893(2)	-1662(1)	33(1)
O(3)	2236(3)	5842(2)	-2186(1)	36(1)
O(4)	942(3)	4807(2)	-2540(1)	34(1)
N(1)	-925(4)	5146(2)	-1913(2)	32(1)
N(2)	507(4)	5990(2)	-1461(2)	32(1)
C(1)	-1262(4)	4962(3)	-1446(2)	34(1)
C(2)	-1320(5)	4320(3)	-1319(2)	44(2)
C(3)	-1695(6)	4156(3)	-871(2)5	2(2)
C(4)	-1986(5)	4613(3)	-532(2)	44(2)
C(5)	-2307(6)	4449(4)	-71(3)	67(2)
C(6)	-2530(7)	4896(4)	269(3)	67(2)
C(7)	-2403(6)	5525(4)	146(3)	59(2)
C(8)	-2113(5)	5700(3)	-298(2)	45(2)
C(9)	-1895(5)	5253(3)	-662(2)	39(2)
C(10)	-1568(5)	5421(2)	-1127(2)	33(1)
C(11)	-1552(5)	6102(3)	-1281(2)	34(1)
C(12)	-2573(6)	6485(2)	-1271(2)	41(1)
C(13)	-3685(5)	6225(3)	-1205(2)	43(2)
C(14)	-4633(6)	6606(3)	-1213(3)	56(2)
C(15)	-4535(7)	7249(3)	-1288(3)	61(2)
C(16)	-3484(6)	7522(3)	-1353(3)	56(2)
C(17)	-2472(6)	7139(3)	-1350(2)	43(2)
C(18)	-1360(6)	7399(3)	-1435(2)	50(2)
C(19)	-409(5)	7030(2)	-1485(2)	39(2)
C(20)	-509(5)	6375(2)	-1411(2)	37(1)
C(21)	-1777(5)	5222(2)	-2210(2)	36(1)
C(22)	-1720(5)	5545(2)	-2659(2)	33(1)
C(23)	-2676(5)	5532(3)	-2957(2)	43(2)
C(24)	-2743(5)	5872(3)	-3360(2)	43(2)
C(25)	-1778(6)	6238(2)	-3477(2)	44(2)
C(26)	-795(5)	6284(2)	-3197(2)	36(1)
C(27)	-761(5)	5936(2)	-2767(2)	34(1)
C(28)	-3797(6)	5871(4)	-3675(3)	58(2)
C(29)	234(5)	6647(2)	-3357(2)	37(2)

C(30)	599(6)	7205(2)	-3120(2)	39(2)
C(31)	1574(6)	7511(3)	-3280(3)	51(2)
C(32)	2216(6)	7309(3)	-3656(3)	51(2)
C(33)	1834(6)	6774(3)	-3900(3)	54(2)
C(34)	838(6)	6461(3)	-3759(2)	44(2)
C(35)	-53(6)	7447(3)	-2698(2)	46(2)
C(36)	3337(7)	7633(4)	-3798(3)	78(2)
C(37)	474(6)	5899(3)	-4055(2)	52(2)
C(38)	1189(5)	5992(2)	-1104(2)	33(1)
C(39)	2159(5)	5567(3)	-1036(2)	37(1)
C(40)	2243(5)	5011(2)	-1312(2)	33(1)
C(41)	3127(5)	4585(3)	-1205(2)	40(2)
C(42)	3889(5)	4716(3)	-840(3)	53(2)
C(43)	3810(6)	5275(3)	-557(2)	50(2)
C(44)	2910(6)	5677(3)	-668(2)	48(2)
C(45)	4636(6)	5384(3)	-155(3)	65(2)
C(46)	3306(5)	3993(2)	-1482(2)	37(2)
C(47)	4254(5)	3895(3)	-1778(2)	43(2)
C(48)	4337(5)	3357(3)	-2048(3)	51(2)
C(49)	3529(6)	2869(3)	-2016(3)	48(2)
C(50)	2627(6)	2950(2)	-1691(2)	43(2)
C(51)	2474(5)	3495(2)	-1433(2)	39(1)
C(52)	5217(6)	4381(3)	-1825(3)	62(2)
C(53)	3645(7)	2278(3)	-2305(3)	71(2)
C(54)	1481(5)	3553(3)	-1104(2)	45(2)
C(55)	2399(7)	6508(3)	-2306(3)	71(2)
C(56)	3536(8)	6591(4)	-2453(4)	106(4)
C(57)	4056(7)	5954(4)	-2537(4)	96(3)
C(58)	3327(5)	5531(3)	-2248(3)	53(2)
C(59)	1173(6)	4910(3)	-3036(2)	47(2)
C(60)	1815(7)	4342(3)	-3203(3)	63(2)
C(61)	1398(13)	3843(4)	-2867(4)	147(6)
C(62)	961(7)	4132(2)	-2454(3)	60(2)
Co(1)	7533(1)	6396(1)	1570(1)	69(1)
O(5)	9858(9)	5891(4)	1432(5)	214(6)
O(6)	7194(7)	6207(2)	2574(2)	97(2)
O(7)	7498(5)	7679(3)	1219(3)	96(2)
O(8)	5713(8)	5682(4)	1109(3)	161(4)
C(63)	8898(9)	6084(5)	1466(4)	119(4)
C(64)	7335(8)	6308(3)	2169(3)	69(2)
C(65)	7500(7)	7171(3)	1367(3)	70(2)
C(66)	6479(10)	5957(5)	1285(3)	115(4)
O(1S)	3495(9)	2080(4)	-69(4)	177(5)
C(1S)	4629(14)	2143(7)	68(7)	210(10)
C(2S)	5039(9)	2757(6)	27(5)	121(4)

C(3S)	4097(11)	3028(5)	-318(5)	122(4)
C(4S)	3302(15)	2506(7)	-370(6)	191(8)
O(2S)	5856(17)	8130(4)	156(4)	182(5)
C(5S)	4741(18)	7929(8)	21(7)	218(11)
C(6S)	4808(14)	7275(10)	79(6)	178(8)
C(7S)	5880(20)	7124(6)	127(8)	198(10)
C(8S)	6539(13)	7681(16)	27(7)	227(12)
O(3S)	-6063(17)	5457(12)	-4947(6)	302(10)
C(9S)	-5767(12)	4754(7)	-4760(5)	143(5)
C(10S)	-6658(13)	4663(10)	-4405(5)	160(6)
C(11S)	-6622(15)	5228(12)	-4188(7)	179(8)
C(12S)	-6473(16)	5707(7)	-4483(8)	182(9)

Table 3.8 Bond lengths [Å] and angles [°] for catalyst (*R*)-6b

Al(1)-O(2)	1.802(4)	C(22)-C(23)	1.388(8)
Al(1)-O(1)	1.814(4)	C(23)-C(24)	1.348(8)
Al(1)-O(4)	1.971(4)	C(24)-C(25)	1.398(9)
Al(1)-O(3)	1.988(4)	C(24)-C(28)	1.507(8)
Al(1)-N(2)	2.015(5)	C(25)-C(26)	1.387(8)
Al(1)-N(1)	2.035(5)	C(26)-C(27)	1.418(8)
O(1)-C(27)	1.326(7)	C(26)-C(29)	1.487(8)
O(2)-C(40)	1.342(7)	C(29)-C(34)	1.388(8)
O(3)-C(58)	1.434(7)	C(29)-C(30)	1.427(8)
O(3)-C(55)	1.468(7)	C(30)-C(31)	1.377(9)
O(4)-C(59)	1.440(7)	C(30)-C(35)	1.495(8)
O(4)-C(62)	1.457(6)	C(31)-C(32)	1.363(9)
N(1)-C(21)	1.302(7)	C(32)-C(33)	1.401(9)
N(1)-C(1)	1.426(7)	C(32)-C(36)	1.521(10)
N(2)-C(38)	1.277(7)	C(33)-C(34)	1.387(9)
N(2)-C(20)	1.438(7)	C(34)-C(37)	1.518(8)
C(1)-C(10)	1.374(8)	C(38)-C(39)	1.453(8)
C(1)-C(2)	1.413(8)	C(39)-C(44)	1.372(8)
C(2)-C(3)	1.378(9)	C(39)-C(40)	1.418(8)
C(3)-C(4)	1.405(9)	C(40)-C(41)	1.398(8)
C(4)-C(5)	1.394(9)	C(41)-C(42)	1.381(9)
C(4)-C(9)	1.413(8)	C(41)-C(46)	1.498(8)
C(5)-C(6)	1.373(11)	C(42)-C(43)	1.434(9)
C(6)-C(7)	1.389(10)	C(43)-C(44)	1.381(9)
C(7)-C(8)	1.345(9)	C(43)-C(45)	1.499(9)
C(8)-C(9)	1.422(9)	C(46)-C(47)	1.391(9)
C(9)-C(10)	1.407(8)	C(46)-C(51)	1.436(8)
C(10)-C(11)	1.513(8)	C(47)-C(48)	1.377(9)
C(11)-C(20)	1.386(8)	C(47)-C(52)	1.524(8)
C(11)-C(12)	1.433(8)	C(48)-C(49)	1.398(9)
C(12)-C(17)	1.415(8)	C(49)-C(50)	1.397(9)
C(12)-C(13)	1.411(9)	C(49)-C(53)	1.504(9)
C(13)-C(14)	1.362(9)	C(50)-C(51)	1.380(8)
C(14)-C(15)	1.389(9)	C(51)-C(54)	1.479(8)
C(15)-C(16)	1.358(10)	C(55)-C(56)	1.388(11)
C(16)-C(17)	1.425(9)	C(56)-C(57)	1.502(11)
C(17)-C(18)	1.418(10)	C(57)-C(58)	1.477(10)
C(18)-C(19)	1.358(8)	C(59)-C(60)	1.493(8)
C(19)-C(20)	1.413(7)	C(60)-C(61)	1.503(11)
C(21)-C(22)	1.440(8)	C(61)-C(62)	1.410(10)
C(22)-C(27)	1.419(8)	Co(1)-C(64)	1.714(8)

Co(1)-C(66)	1.732(9)	C(21)-N(1)-C(1)	114.8(5)
Co(1)-C(63)	1.735(10)	C(21)-N(1)-Al(1)	124.0(4)
Co(1)-C(65)	1.746(7)	C(1)-N(1)-Al(1)	119.9(4)
O(5)-C(63)	1.187(10)	C(38)-N(2)-C(20)	115.1(5)
O(6)-C(64)	1.171(8)	C(38)-N(2)-Al(1)	124.0(4)
O(7)-C(65)	1.156(7)	C(20)-N(2)-Al(1)	120.7(4)
O(8)-C(66)	1.170(9)	C(10)-C(1)-N(1)	118.7(5)
O(1S)-C(4S)	1.260(12)	C(10)-C(1)-C(2)	120.5(6)
O(1S)-C(1S)	1.372(14)	N(1)-C(1)-C(2)	120.8(5)
C(1S)-C(2S)	1.394(14)	C(3)-C(2)-C(1)	119.5(6)
C(2S)-C(3S)	1.569(16)	C(2)-C(3)-C(4)	121.5(6)
C(3S)-C(4S)	1.448(16)	C(5)-C(4)-C(9)	120.2(6)
O(2S)-C(8S)	1.29(2)	C(5)-C(4)-C(3)	121.6(6)
O(2S)-C(5S)	1.41(2)	C(9)-C(4)-C(3)	118.1(6)
C(5S)-C(6S)	1.40(2)	C(6)-C(5)-C(4)	121.7(7)
C(6S)-C(7S)	1.29(2)	C(5)-C(6)-C(7)	118.2(7)
C(7S)-C(8S)	1.43(3)	C(8)-C(7)-C(6)	121.6(7)
O(3S)-C(9S)	1.62(2)	C(7)-C(8)-C(9)	122.0(6)
O(3S)-C(12S)	1.49(2)	C(4)-C(9)-C(10)	120.4(5)
C(9S)-C(10S)	1.448(17)	C(4)-C(9)-C(8)	116.3(6)
C(10S)-C(11S)	1.35(2)	C(10)-C(9)-C(8)	123.3(5)
C(11S)-C(12S)	1.33(2)	C(1)-C(10)-C(9)	119.9(5)
		C(1)-C(10)-C(11)	119.3(5)
O(2)-Al(1)-O(1)	170.8(2)	C(9)-C(10)-C(11)	120.8(5)
O(2)-Al(1)-O(4)	85.26(17)	C(20)-C(11)-C(12)	118.9(5)
O(1)-Al(1)-O(4)	88.68(17)	C(20)-C(11)-C(10)	119.2(5)
O(2)-Al(1)-O(3)	88.48(16)	C(12)-C(11)-C(10)	121.9(5)
O(1)-Al(1)-O(3)	84.73(16)	C(17)-C(12)-C(13)	118.8(6)
O(4)-Al(1)-O(3)	91.66(17)	C(17)-C(12)-C(11)	119.2(6)
O(2)-Al(1)-N(2)	87.93(18)	C(13)-C(12)-C(11)	122.0(5)
O(1)-Al(1)-N(2)	98.51(18)	C(14)-C(13)-C(12)	119.7(6)
O(4)-Al(1)-N(2)	172.29(18)	C(13)-C(14)-C(15)	121.6(7)
O(3)-Al(1)-N(2)	91.77(17)	C(16)-C(15)-C(14)	121.0(6)
O(2)-Al(1)-N(1)	99.02(18)	C(15)-C(16)-C(17)	119.2(6)
O(1)-Al(1)-N(1)	88.12(18)	C(18)-C(17)-C(12)	119.0(6)
O(4)-Al(1)-N(1)	91.85(17)	C(18)-C(17)-C(16)	121.3(5)
O(3)-Al(1)-N(1)	171.96(17)	C(12)-C(17)-C(16)	119.7(6)
N(2)-Al(1)-N(1)	85.65(19)	C(19)-C(18)-C(17)	121.7(6)
C(27)-O(1)-Al(1)	132.3(3)	C(20)-C(19)-C(18)	119.2(6)
C(40)-O(2)-Al(1)	128.8(3)	C(19)-C(20)-C(11)	121.5(5)
C(58)-O(3)-C(55)	107.7(4)	C(19)-C(20)-N(2)	118.6(5)
C(58)-O(3)-Al(1)	126.9(3)	C(11)-C(20)-N(2)	119.9(5)
C(55)-O(3)-Al(1)	125.1(4)	N(1)-C(21)-C(22)	126.0(5)
C(59)-O(4)-C(62)	108.0(4)	C(27)-C(22)-C(23)	120.1(5)
C(59)-O(4)-Al(1)	128.1(3)	C(27)-C(22)-C(21)	120.3(5)
C(62)-O(4)-Al(1)	123.7(4)	C(23)-C(22)-C(21)	119.1(5)

C(24)-C(23)-C(22)	123.0(6)
C(23)-C(24)-C(25)	116.9(6)
C(23)-C(24)-C(28)	122.8(6)
C(25)-C(24)-C(28)	120.3(6)
C(26)-C(25)-C(24)	123.8(6)
C(25)-C(26)-C(27)	118.2(6)
C(25)-C(26)-C(29)	121.2(5)
C(27)-C(26)-C(29)	120.5(5)
O(1)-C(27)-C(22)	121.5(5)
O(1)-C(27)-C(26)	120.6(5)
C(22)-C(27)-C(26)	117.9(5)
C(34)-C(29)-C(30)	118.1(5)
C(34)-C(29)-C(26)	120.1(5)
C(30)-C(29)-C(26)	121.8(6)
C(31)-C(30)-C(29)	118.8(6)
C(31)-C(30)-C(35)	120.7(5)
C(29)-C(30)-C(35)	120.6(5)
C(30)-C(31)-C(32)	123.4(6)
C(31)-C(32)-C(33)	117.9(6)
C(31)-C(32)-C(36)	121.6(7)
C(33)-C(32)-C(36)	120.5(7)
C(34)-C(33)-C(32)	120.6(6)
C(29)-C(34)-C(33)	121.0(6)
C(29)-C(34)-C(37)	122.3(5)
C(33)-C(34)-C(37)	116.7(6)
N(2)-C(38)-C(39)	125.2(5)
C(44)-C(39)-C(40)	120.9(5)
C(44)-C(39)-C(38)	118.7(5)
C(40)-C(39)-C(38)	120.0(5)
O(2)-C(40)-C(41)	120.9(5)
O(2)-C(40)-C(39)	121.0(5)
C(41)-C(40)-C(39)	118.1(5)
C(40)-C(41)-C(42)	119.8(6)
C(40)-C(41)-C(46)	122.2(5)
C(42)-C(41)-C(46)	118.0(5)
C(41)-C(42)-C(43)	122.6(6)
C(44)-C(43)-C(42)	115.8(6)
C(44)-C(43)-C(45)	123.7(6)
C(42)-C(43)-C(45)	120.4(6)
C(43)-C(44)-C(39)	122.8(6)
C(47)-C(46)-C(51)	118.3(5)
C(47)-C(46)-C(41)	123.2(5)
C(51)-C(46)-C(41)	118.5(5)
C(46)-C(47)-C(48)	120.6(5)
C(46)-C(47)-C(52)	121.6(5)
C(48)-C(47)-C(52)	117.7(6)
C(47)-C(48)-C(49)	122.3(6)
C(50)-C(49)-C(48)	116.7(6)
C(50)-C(49)-C(53)	121.5(6)
C(48)-C(49)-C(53)	121.8(6)
C(51)-C(50)-C(49)	122.9(5)
C(50)-C(51)-C(46)	118.9(6)
C(50)-C(51)-C(54)	119.9(5)
C(46)-C(51)-C(54)	121.2(5)
C(56)-C(55)-O(3)	108.2(6)
C(55)-C(56)-C(57)	108.1(7)
C(58)-C(57)-C(56)	103.6(6)
O(3)-C(58)-C(57)	106.7(5)
O(4)-C(59)-C(60)	105.9(5)
C(61)-C(60)-C(59)	102.4(6)
C(62)-C(61)-C(60)	109.1(6)
C(61)-C(62)-O(4)	107.3(6)
C(64)-Co(1)-C(66)	107.7(4)
C(64)-Co(1)-C(63)	104.3(5)
C(66)-Co(1)-C(63)	110.7(6)
C(64)-Co(1)-C(65)	115.0(4)
C(66)-Co(1)-C(65)	110.0(5)
C(63)-Co(1)-C(65)	109.0(4)
O(5)-C(63)-Co(1)	174.3(12)
O(6)-C(64)-Co(1)	175.7(6)
O(7)-C(65)-Co(1)	177.8(8)
O(8)-C(66)-Co(1)	175.6(11)
C(4S)-O(1S)-C(1S)	106.8(11)
O(1S)-C(1S)-C(2S)	113.1(11)
C(1S)-C(2S)-C(3S)	99.2(9)
C(4S)-C(3S)-C(2S)	102.8(9)
O(1S)-C(4S)-C(3S)	111.8(11)
C(8S)-O(2S)-C(5S)	104.9(12)
C(6S)-C(5S)-O(2S)	102.7(11)
C(5S)-C(6S)-C(7S)	108.2(15)
C(6S)-C(7S)-C(8S)	106.4(16)
O(2S)-C(8S)-C(7S)	103.5(15)
C(9S)-O(3S)-C(12S)	96.4(10)
O(3S)-C(9S)-C(10S)	101.4(13)
C(9S)-C(10S)-C(11S)	99.9(16)
C(12S)-C(11S)-C(10S)	113.8(18)
C(11S)-C(12S)-O(3S)	108.5(14)

Symmetry transformations used to generate equivalent atoms.

Table 3.9 Anisotropic displacement parameters ($Å^2$ x 10^3) for catalyst (*R*)-6b

The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [h^2 $a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Al(1)	26(1)	18(1)	47(1)	1(1)	-1(1)	1(1)
O(1)	27(2)	21(2)	47(2)	2(2)	-5(2)	-1(2)
O(2)	31(2)	18(2)	50(3)	3(2)	-6(2)	0(2)
O(3)	25(2)	23(2)	61(3)	7(2)	3(2)	-2(2)
O(4)	37(2)	18(2)	48(2)	0(2)	3(2)	4(2)
N(1)	35(3)	16(2)	46(3)	0(2)	1(3)	1(2)
N(2)	26(3)	24(2)	45(3)	2(2)	1(2)	-2(2)
C(1)	14(3)	36(3)	53(4)	7(3)	3(3)	0(2)
C(2)	36(4)	27(3)	68(5)	8(3)	0(3)	-2(3)
C(3)	49(4)	41(4)	65(5)	26(4)	3(4)	-1(3)
C(4)	32(3)	47(4)	52(4)	22(3)	2(3)	11(3)
C(5)	58(5)	73(5)	71(5)	39(4)	5(4)	17(4)
C(6)	57(5)	84(6)	59(5)	25(4)	2(4)	12(5)
C(7)	46(4)	77(5)	54(5)	1(4)	-5(4)	11(4)
C(8)	38(4)	48(4)	49(4)	9(3)	-4(3)	6(3)
C(9)	29(3)	43(3)	46(4)	11(3)	0(3)	3(3)
C(10)	29(3)	29(3)	42(4)	3(3)	1(3)	8(3)
C(11)	31(3)	33(3)	39(4)	4(2)	2(3)	-2(3)
C(12)	42(4)	35(3)	45(4)	4(3)	1(3)	16(3)
C(13)	23(3)	49(4)	57(4)	9(3)	4(3)	2(3)
C(14)	29(4)	65(5)	74(5)	13(4)	5(3)	11(3)
C(15)	47(5)	53(4)	83(6)	17(4)	8(4)	23(4)
C(16)	50(5)	47(4)	71(5)	16(3)	18(4)	23(3)
C(17)	44(4)	37(3)	49(4)	5(3)	5(3)	3(3)
C(18)	66(5)	23(3)	62(5)	-1(3)	6(4)	17(3)
C(19)	38(4)	22(3)	56(4)	4(3)	-1(3)	-2(3)
C(20)	41(4)	25(3)	43(4)	7(3)	-4(3)	8(3)
C(21)	27(3)	23(3)	56(4)	1(3)	3(3)	-2(2)
C(22)	31(3)	16(3)	52(4)	-2(2)	-3(3)	2(2)
C(23)	38(4)	35(3)	55(4)	-2(3)	-1(3)	6(3)
C(24)	32(4)	41(3)	55(4)	-7(3)	-6(3)	7(3)
C(25)	58(4)	24(3)	48(4)	-3(3)	-11(3)	11(3)
C(26)	43(4)	18(3)	46(4)	2(2)	2(3)	5(3)
C(27)	40(4)	21(3)	41(4)	-7(2)	-5(3)	8(3)
C(28)	32(4)	83(5)	60(5)	1(4)	-14(3)	7(4)

C(29)	45(4)	19(3)	47(4)	5(3)	-3(3)	1(2)
C(30)	51(4)	21(3)	44(4)	9(3)	2(3)	4(3)
C(31)	67(5)	23(3)	64(5)	4(3)	-6(4)	-7(3)
C(32)	46(4)	49(4)	59(5)	14(3)	4(4)	-11(3)
C(33)	64(5)	41(4)	55(5)	0(3)	13(4)	1(3)
C(34)	51(4)	31(3)	50(4)	3(3)	4(3)	-5(3)
C(35)	49(4)	28(3)	61(5)	-3(3)	-4(3)	6(3)
C(36)	57(5)	80(5)	96(7)	11(5)	13(5)	-14(4)
C(37)	58(5)	36(3)	63(5)	-8(3)	7(4)	-3(3)
C(38)	29(3)	27(3)	44(4)	1(3)	0(3)	3(2)
C(39)	24(3)	36(3)	50(4)	6(3)	-4(3)	-6(3)
C(40)	27(3)	20(3)	52(4)	9(2)	1(3)	0(2)
C(41)	30(3)	28(3)	62(4)	5(3)	-4(3)	-7(3)
C(42)	31(4)	41(4)	88(5)	17(4)	-15(4)	-8(3)
C(43)	44(4)	35(3)	70(5)	9(3)	-22(4)	-5(3)
C(44)	45(4)	37(3)	61(4)	6(3)	-11(3)	-4(3)
C(45)	49(4)	53(4)	92(6)	13(4)	-38(4)	-8(3)
C(46)	22(3)	26(3)	63(4)	9(3)	-12(3)	3(2)
C(47)	20(3)	27(3)	81(5)	10(3)	-4(3)	6(3)
C(48)	29(3)	42(4)	83(5)	6(3)	5(4)	6(3)
C(49)	47(4)	27(3)	70(5)	11(3)	0(4)	8(3)
C(50)	39(4)	24(3)	66(4)	12(3)	-1(4)	-6(3)
C(51)	28(3)	25(3)	64(4)	8(3)	-4(3)	-2(3)
C(52)	32(4)	42(4)	112(6)	15(4)	5(4)	-7(3)
C(53)	57(5)	41(4)	114(7)	-4(4)	22(5)	0(4)
C(54)	37(4)	27(3)	71(5)	9(3)	-1(3)	-3(3)
C(55)	53(5)	29(3)	131(7)	13(4)	10(5)	-10(3)
C(56)	64(6)	58(5)	198(11)	53(6)	34(7)	10(4)
C(57)	42(5)	70(5)	176(10)	22(6)	45(6)	-4(4)
C(58)	21(3)	47(4)	90(5)	8(4)	17(3)	8(3)
C(59)	66(5)	28(3)	47(4)	4(3)	3(4)	2(3)
C(60)	81(5)	42(4)	65(5)	-8(3)	25(4)	11(4)
C(61)	291(17)	31(4)	118(8)	9(5)	118(10)	32(7)
C(62)	89(6)	13(3)	77(5)	2(3)	15(4)	3(3)
Co(1)	67(1)	56(1)	84(1)	-15(1)	27(1)	-17(1)
O(5)	166(9)	116(6)	361(17)	-6(8)	142(10)	68(6)
O(6)	148(6)	58(3)	84(4)	-7(3)	21(4)	31(4)
O(7)	64(4)	64(4)	159(6)	14(4)	4(4)	7(3)
O(8)	177(8)	192(8)	114(6)	-46(6)	49(6)	-138(8)
C(63)	135(10)	77(6)	144(10)	-33(6)	67(8)	0(6)
C(64)	81(6)	49(4)	78(6)	-16(4)	7(5)	8(4)
C(65)	39(4)	60(5)	111(7)	0(4)	8(5)	2(4)
C(66)	160(11)	101(7)	84(7)	-29(6)	37(7)	-83(8)
O(1S)	143(8)	110(6)	279(12)	105(7)	-86(8)	-43(6)
C(1S)	146(13)	135(12)	350(30)	133(14)	-141(16)	-57(10)

C(2S)	88(8)	143(10)	132(10)	-51(8)	24(7)	-13(8)
C(3S)	127(10)	70(7)	171(12)	39(7)	-4(9)	15(7)
C(4S)	219(17)	129(11)	226(16)	104(12)	-131(14)	-57(11)
O(2S)	299(18)	66(5)	183(10)	-28(5)	-36(12)	-39(8)
C(5S)	225(19)	125(11)	300(20)	-133(14)	-150(17)	127(13)
C(6S)	102(11)	290(30)	141(13)	-67(15)	-2(10)	-51(14)
C(7S)	230(20)	76(8)	290(20)	-20(10)	-150(20)	14(11)
C(8S)	86(11)	440(40)	154(15)	-100(20)	25(10)	-40(18)
O(3S)	310(20)	400(20)	201(14)	114(16)	5(14)	-148(19)
C(9S)	113(10)	180(13)	134(11)	-38(10)	36(9)	-14(10)
C(10S)	103(11)	270(20)	107(11)	12(12)	0(9)	15(13)
C(11S)	118(12)	260(20)	159(17)	-60(18)	10(11)	43(15)
C(12S)	225(19)	101(10)	221(19)	14(11)	117(16)	94(11)

Table 3.10 Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for catalyst (*R*)-6b

	x	y	z	U(eq)
H(2A)	-1102	4004	-1540	53
H(3A)	-1758	3723	-791	62
H(5A)	-2373	4017	10	81
H(6A)	-2765	4779	579	80
H(7A)	-2523	5839	380	71
H(8A)	-2052	6135	-369	54
H(13A)	-3773	5785	-1155	52
H(14A)	-5378	6428	-1166	67
H(15A)	-5213	7502	-1294	73
H(16A)	-3425	7963	-1401	67
H(18A)	-1279	7842	-1457	60
H(19A)	316	7209	-1569	46
H(21A)	-2504	5047	-2123	43
H(23A)	-3313	5272	-2874	51
H(25A)	-1798	6469	-3766	52
H(28A)	-4388	5594	-3540	87
H(28B)	-3583	5720	-3992	87
H(28C)	-4105	6299	-3700	87
H(31A)	1813	7882	-3120	62
H(33A)	2261	6623	-4165	64
H(35A)	475	7484	-2427	69
H(35B)	-679	7154	-2620	69
H(35C)	-380	7860	-2773	69
H(36A)	3469	7997	-3592	117
H(36B)	3282	7774	-4129	117
H(36C)	3984	7338	-3766	117
H(37A)	-240	5720	-3925	78
H(37B)	1087	5581	-4049	78
H(37C)	340	6033	-4383	78
H(38A)	1050	6296	-863	40
H(42A)	4489	4423	-773	64
H(44A)	2806	6044	-481	57
H(45A)	4489	5798	-15	97
H(45B)	5433	5368	-275	97
H(45C)	4527	5058	86	97
H(48A)	4966	3315	-2263	61
H(50A)	2096	2614	-1646	52
H(52A)	5047	4741	-1619	93

H(52B)	5268	4522	-2155	93
H(52C)	5955	4192	-1729	93
H(53A)	4050	1957	-2118	106
H(53B)	4086	2368	-2594	106
H(53C)	2873	2123	-2390	106
H(54A)	981	3899	-1208	67
H(54B)	1766	3638	-783	67
H(54C)	1038	3160	-1104	67
H(55A)	1860	6632	-2562	85
H(55B)	2239	6773	-2024	85
H(56A)	3980	6818	-2206	128
H(56B)	3556	6842	-2749	128
H(57A)	4020	5839	-2878	115
H(57B)	4873	5941	-2431	115
H(58A)	3218	5124	-2412	63
H(58B)	3695	5451	-1937	63
H(59A)	1648	5293	-3081	57
H(59B)	440	4960	-3215	57
H(60A)	1614	4238	-3536	75
H(60B)	2662	4403	-3178	75
H(61A)	782	3590	-3020	176
H(61B)	2045	3559	-2783	176
H(62A)	1463	4035	-2178	72
H(62B)	170	3977	-2385	72
H(1SA)	5116	1863	-130	252
H(1SB)	4706	2005	402	252
H(2SA)	5823	2772	-114	145
H(2SB)	5042	2978	337	145
H(3SA)	3707	3399	-178	147
H(3SB)	4441	3148	-627	147
H(4SA)	2499	2660	-331	230
H(4SB)	3376	2329	-694	230
H(5SA)	4139	8113	229	262
H(5SB)	4572	8042	-313	262
H(6SA)	4476	7061	-201	214
H(6SB)	4365	7145	363	214
H(7SA)	6092	6784	-97	237
H(7SB)	6036	6978	455	237
H(8SA)	7268	7688	212	272
H(8SB)	6725	7711	-315	272
H(9SA)	-4983	4732	-4618	171
H(9SB)	-5829	4440	-5018	171
H(10A)	-6464	4317	-4184	192
H(10B)	-7424	4582	-4551	192
H(11A)	-7353	5291	-4011	215

H(11B)	-5981	5227	-3954	215
H(12A)	-5896	6003	-4352	219
H(12B)	-7213	5935	-4527	219

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CHAPTER FOUR

A Catalytic Route to Ampakines and Their Derivatives Using Hydroformylation

4.1 Introduction

Neurodegenerative diseases such as Alzheimer's or Parkinson's are on the rise globally and will lead to substantial financial and societal costs if effective treatments are not found in the near future.[1] One promising therapy currently under investigation is the administration of ampakines.[2] These compounds allow positive allosteric modulation of AMPA receptors and could help alleviate the symptoms of these diseases by restoring diminished glutamatergic neurotransmission.[2b,d] Important examples of ampakines are CX-554[3] and CX-614[4] (Figure 4.1), and their effects on cell receptors and potential medicinal applications are well documented. Structurally related to CX-614, 3-substituted-[1,2,3]-benzotriazinones (Figure 4.1) also show potential for the treatment of neurodegenerative diseases by modulating AMPA receptors at nanomolar concentrations.[5a]

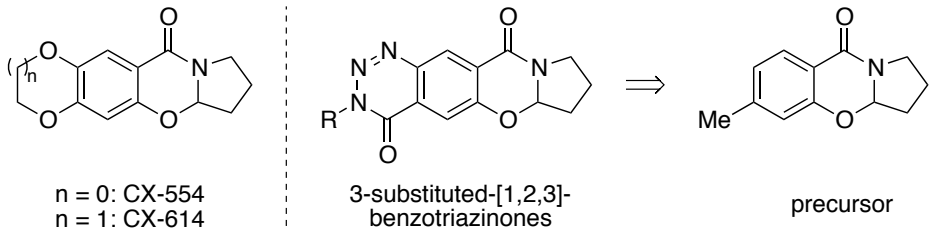


Figure 4.1 Examples of ampakines

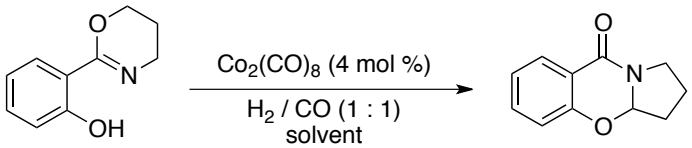
As part of research efforts focused on the use of carbon monoxide as a feedstock for the preparation of synthetically useful intermediates,[6] our group recently reported the carbonylative ring-expansion of 2-substituted oxazolines to oxazinones[7,8] and hydroformylation of 2-oxazolines to *N*-acylated aminoaldehydes.[9] Based on these findings we proposed that the *in situ* generation of an aminoaldehyde moiety followed

by cyclization could produce the desired ampakine targets or synthetic precursors shown in Figure 4.1. This methodology would be very atom economical, as opposed to current synthetic routes, which use hard-to-obtain precursors,[5] suffer from low yields,[10] or require stoichiometric,[11] toxic,[12] or expensive[13] reagents. In this report we describe a domino reaction[14] that readily yields the desired ampakine framework while using simple starting materials and $Co_2(CO)_8$ as an inexpensive precatalyst.

4.2 Reaction Development

We hypothesized that a dihydrooxazine bearing an *ortho*-substituted phenol would give the desired ampakine structure following stepwise hydroformylation and cyclization. To test this theory, a model substrate was synthesized and subjected to hydroformylation conditions in the presence of catalytic amounts of $Co_2(CO)_8$ (Table 4.1). Solvents of different polarities and Lewis-basicities were investigated as these parameters are crucial in related carbonylation reactions.[15] Toluene proved to be the best solvent (entry 9), yielding the desired product in 81% isolated yield. Highly polar and completely non-polar solvents both impeded the reaction (entries 1-3). Benzene as solvent gave results similar to those obtained with toluene (entry 8), but was not pursued further due to its higher toxicity. Lowering the reaction temperature or the overall pressure decreased the yield (entries 10 and 11). Furthermore, adding molecular sieves (3Å) to the reaction mixture led to no improvement, suggesting that the water produced in the reaction has no deleterious effect.

Table 4.1 Influence of solvent, pressure, and temperature[a]



1a **2a**

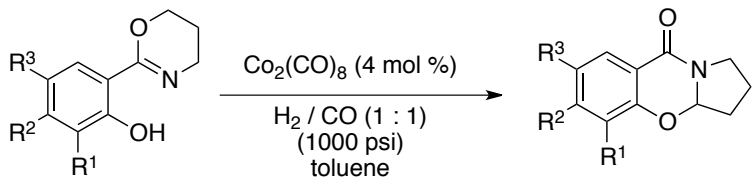
entry	solvent	pressure (psi)	temperature (°C)	isol. yield (%)
1	DMF	1000	80	<1[b]
2	MeCN	1000	80	<1[b]
3	hexanes	1000	80	<1[b]
4	THF	1000	80	50
5	MTBE	1000	80	58
6	EtOAc	1000	80	65
7	1,4-Dioxane	1000	80	70
8	benzene	1000	80	79
9	toluene	1000	80	81
10	toluene	1000	60	23[b]
11	toluene	800	80	61[b]

[a]Reaction conditions: [**1a**] = 0.25 M, 20 h. Isolated yield for reactions carried out on a 0.5 mmol scale.
[b]Determined by ^{1}H NMR spectroscopy.

4.3 Scope of the Reaction

Next, we subjected a variety of substituted dihydrooxazines to the optimized conditions (Table 4.2). The introduction of either electron-withdrawing (entry 2) or electron-donating (entries 3, 4, 6, 7, 9, and 10) substituents onto the aryl-moiety of the dihydrooxazine decreased the isolated yield in comparison to the unsubstituted substrate (entry 1), despite complete consumption of the corresponding starting materials.[16] The decrease in yield in entry 2 is consistent with observations made by Jia and coworkers for the carbonylative ring-expansion of aryl-substituted 2-

Table 4.2 Hydroformylation of substituted 2-aryl-dihydrooxazines[a]



1b-k **2b-k**

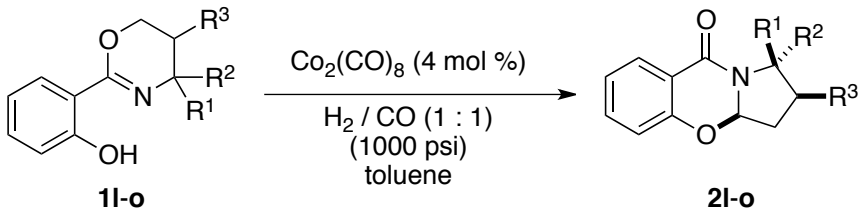
entry	R^1	R^2	R^3	isol. product	isol. yield (%)
1	H	H	H	**2a**	81, 81[b]
2	H	H	F	**2b**	65
3	H	H	Me	**2c**	70, 73[c]
4	H	H	OMe	**2d**	68, 87[c]
5	H	H	Ph	**2e**	72[c]
6	H	Me	H	**2f**	72[c]
7	H	OMe	H	**2g**	43, 73[c], 74[d]
8	Br	H	H	**2h**	79
9	H	(-OCH_2O-)		**2i**	76[c]
10	H	(-OCH_2CH_2O-)		**2j**	40, 71[c]
11	H	(-CH=CH-)$_2$		**2k**	64, 80[c]

[a]Reaction conditions: [**1**] = 0.25 M, 80 °C, 20 h. Isolated yield for reactions carried out on a 0.5 mmol scale. [b]7.5 mmol scale. [c][**1**] = 0.12 M, 0.4 mmol scale. [d]8 mol % $Co_2(CO)_8$, [**1**] = 0.12 M, 0.4 mmol scale.

oxazolines.[8] In entries 3, 4, 6, 7, 9, and 10 the electron-donating substituents should increase the nucleophilicity of the dihydrooxazine, which could facilitate initiation of unproductive ring-opening polymerization, a well-known reaction of oxazolines and oxazines.[17] Initiation of polymerization requires the attack of a substrate molecule on an already activated substrate molecule (Scheme 4.1, path A: S_N2 attack by **1a** in the place of $Co(CO)_4^-$; and path B: attack by **1a** at Co-acyl **C**).[17a] Consequently, we decided to decrease the overall substrate concentration to favor the desired hydrofor-

mylation pathway. This modification of the reaction conditions led to a pronounced increase in yield for substrates with electron-donating substituents (entries 4, 6, and 11), and furnished CX-554[3] (entry 9), CX-614[4] (entry 10) and the intermediate needed for the synthesis of benzotriazinones (entry 6) in good yield. Lastly, our methodology scales very well as can be seen in entry 1. Increasing the scale of the reaction by more than an order of magnitude had no impact on the quantity or quality of the product **2a**.

Table 4.3 Hydroformylation of alkylsubstituted 2-dihydrooxazines



1l-o **2l-o**

entry	R^1	R^2	R^3	isol. product	isol. yield (%)[a]	dr[c]
1	Me	H	H	**2l**	66, 90[b]	1.6 : 1
2	Ph	H	H	**2m**	80	2.9 : 1
3	Me	Me	H	**2n**	93	-
4	H	H	Me	**2o**	80	1.3 : 1

[a]Reaction conditions: [**1**] = 0.25 M, 80 °C, 20 h. Isolated yield for reactions carried out on a 0.5 mmol scale. [b][**1**] = 0.12 M, 0.4 mmol scale. [c]Diastereomeric ratio (*cis* : *trans*).

Modifications to the dihydrooxazine backbone were well tolerated (Table 4.3, entries 1-4).[18] The observed diastereomeric ratios in favor of *cis*-configuration were relatively small, possibly due to the flexibility of the five-membered ring and the distance between the existing and the newly formed stereocenter. The position of the substituent had little effect on the ratio (entries 1 and 4), whereas changing the size of the substituent from methyl to phenyl roughly doubled the stereoselectivity (entries 1 and 2). Furthermore, the diastereomeric ratios seem to be primarily kinetically controlled.

For example, in entry 1 the *cis*-isomer forms in 23% excess; a pure sample of this diastereomer is recovered unchanged when resubjected to our hydroformylation conditions, but epimerizes to approximately a 1 : 1 mixture when exposed to *p*-toluenesulfonic acid at 40 °C. Consequently, the two diastereomers of a given substrate seemingly do not interconvert under our reaction conditions. Lastly, the *cis*-configuration in the major isomer of **2m** was confirmed crystallographically (Figure 4.2), and presumably is analogous for the major isomers of products **2l** and **2o**.

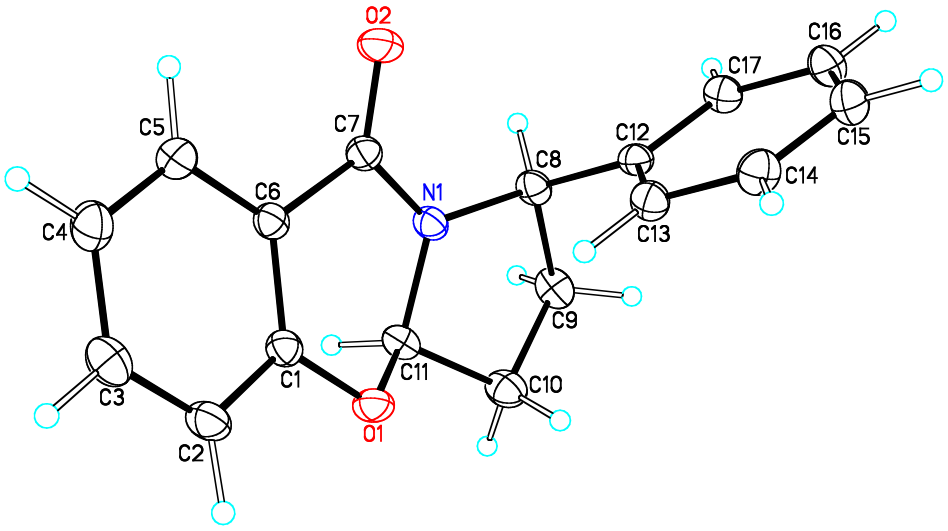
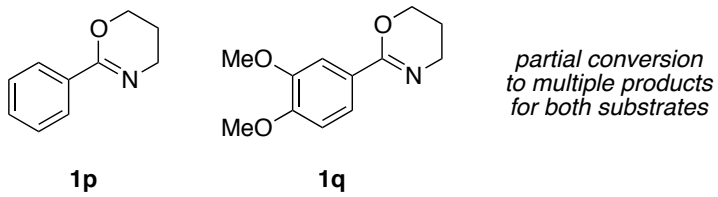


Figure 4.2 ORTEP-representation of 2m with thermal ellipsoids drawn at 50% probability

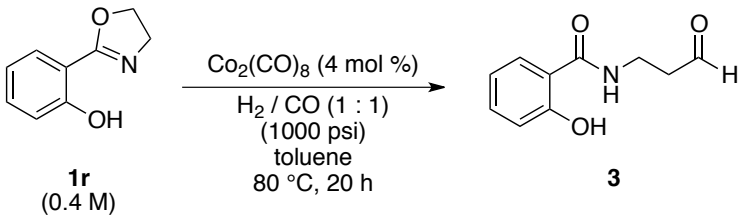
Although our methodology turned out to be quite general as was seen in Table 4.2 and Table 4.3, some substrates did not furnish the desired products when using standard reaction conditions. For example, **1p** and **1q** (Figure 4.3) both gave low conversions to a multitude of products. For these substrates, one may have hoped for clean conversion to an amido-aldehyde containing product analogous to that seen in



1p **1q**

Figure 4.3 Substrates that were not amenable to hydroformylation reactions

Equation 4.1,[9] or a Friedel-Crafts-type reaction of the postulated intermediary acyl-cobalt species **C** (Scheme 4.1). In addition, oxazolin **1r** gave the expected product **3** (equation 4.1),[9] and no further ring-closing reaction was observed.



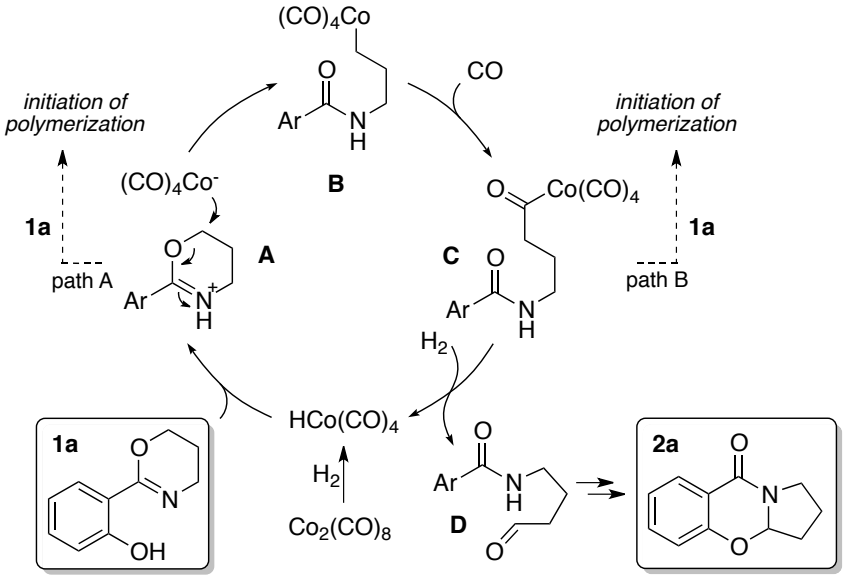
1r
(0.4 M)

3

(4.1)

4.4 Proposed Catalytic Cycle

Based on previous literature reports,[7,8,13] we expect the first part of the domino reaction to proceed by the catalytic cycle depicted in Scheme 4.1.



Scheme 4.1 Proposed catalytic cycle for the conversion of dihydrooxazine 1a to 2a

First, activation of the dihydrooxazine **1a** through protonation and subsequent ring-opening *via* an S_N2-type pathway (**A**) should give rise to a transient cobalt-alkyl species **B**. Insertion of CO,[19] followed by hydrogenolysis of the resulting cobalt-acyl intermediate **C**[20,21] produces an *N*-acylaminoaldehyde **D**. The presence of the Brønsted-acid $HCo(CO)_4$ should then facilitate isomerization to the corresponding hemiaminal and subsequent formation of an iminium ion by loss of water. A fast second cyclization to the final product **2a** is likely given the close vicinity of the phenol-group to the iminium ion.

4.5 Conclusion

In conclusion, we have developed an atom economical route to an important ampakine framework *via* hydroformylation of dihydrooxazines. Our methodology provides quick access to the pharmaceutically interesting compound CX-614 (Table 4.2, entry 10) and to a central building block for the synthesis of 3-substituted-[1,2,3]-benzotriazinones (Table 4.2, entry 6). In both cases, the modular nature of the starting materials allows for the synthesis of a wide range of derivatives.

4.6 Experimental Procedures

4.6.1 General Considerations

Unless stated otherwise all synthetic manipulations were carried out using standard Schlenk techniques under a nitrogen atmosphere or in an MBraun Unilab glovebox under an atmosphere of purified nitrogen. Reactions were carried out in oven-dried glassware cooled under vacuum. Anhydrous toluene, hexanes and tetrahydrofuran were purchased from Fischer Scientific and sparged vigorously with nitrogen for 40 minutes prior to first use. The solvents were further purified by passing them under nitrogen pressure through two packed columns of neutral alumina (tetrahydrofuran was also passed through a third column packed with activated 4Å molecular sieves) or through neutral alumina and copper(II) oxide (for toluene and hexanes). Chlorobenzene was distilled from phosphorus pentoxide and degassed *via* three freeze-pump-thaw cycles prior to use. All non-dried solvents used were reagent grade or better and used as received.

IR spectra were recorded on a Nicolet 380 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz instrument with shifts reported relative to the residual solvent peak. ^{19}F NMR spectra were recorded on a Varian 400 MHz instrument with shifts referenced to an external standard of neat $CFCl_3$ (0 ppm). NMR solvents were purchased from Cambridge Isotope Laboratories and used as received.

Carbon monoxide (Matheson, 99.99% min. purity) and hydrogen (Airgas, 99.999% min. purity) were used as received. Dicobalt octacarbonyl (Strem Chemicals, stabilized with 1-5% hexanes) was stored at –35 °C in a glove box freezer and used as received. Zinc chloride (Strem Chemicals, anhydrous) was stored in a glove box and used as received. All other chemicals were purchased from Aldrich or Alfa-Aesar and used as received. Flash column chromatography was performed with silica gel (particle size 40-64 μm, 230-400 mesh) using mixtures of ethyl acetate and hexanes as eluent unless stated otherwise.

The starting materials 3-hydroxy-2-naphthonitrile,[22] 6-hydroxybenzo[*d*][1,3]dioxole-5-carbaldehyde,[23] dihydro-2,3-formyl-7-hydroxy-6-benzodioxane-1,4,[24] 3-amino-3-phenylpropan-1-ol,[25] 3-amino-3-methylbutanoic acid,[26] 3-amino-2-methylpropan-1-ol,[27] 2-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (**1a**),[28] 2-phenyl-5,6-dihydro-4H-1,3-oxazine (**1p**),[29] and 2-(4,5-dihydrooxazol-2-yl)phenol (**1r**)[30] were prepared according to literature procedures. The following previously synthesized amino alcohols were obtained by reduction of the corresponding amino acids with lithium aluminum hydride according to a published procedure,[4] and their analytical

data compared to that found in the literature: 3-aminobutan-1-ol[31] and 3-amino-3-methylbutan-1-ol.[32]

4.6.2 Synthetic Procedures

4.6.2.1 Preparation of 2-Hydroxybenzonitriles

General Procedure A: Synthesis of 2-Hydroxybenzonitriles from the corresponding 2-Hydroxybenzaldehydes

2-Hydroxybenzonitriles were synthesized from the corresponding 2-hydroxybenzaldehydes using a modified published procedure:[33] A round-bottom flask was charged with the appropriate 2-hydroxybenzaldehyde (7.0 mmol), nitroethane (14.0 mmol), glacial acetic acid (1.5 ml) and anhydrous sodium acetate (14.0 mmol) and the resulting mixture was refluxed until TLC analysis indicated complete consumption of the 2-hydroxybenzaldehyde. Upon cooling the reaction mixture for five minutes water and ethyl acetate were added and the resulting layers separated. The aqueous layer was extracted two times with ethyl acetate and the combined organic layers were washed two times with saturated aqueous sodium bicarbonate solution, then with brine, then dried with sodium sulfate, filtered and concentrated under reduced pressure. The residue was then purified *via* flash column chromatography.

Using this procedure the following 2-hydroxybenzonitriles were obtained and their analytical data compared to that found in the literature: 2-hydroxy-5-methyl-benzonitrile,[34] 2-hydroxy-5-methoxybenzonitrile,[35] 2-hydroxy-4-methoxy-benzonitrile,[36] 4-hydroxy-[1,1'-biphenyl]-3-carbonitrile.[37] 2-Hydroxy-4-methyl-

benzonitrile contained an inseparable impurity after flash column chromatography and thus was used for the next reaction without further purification.

5-Fluoro-2-hydroxybenzonitrile

Lithium chloride (0.636 g, 15.0 mmol) was placed in a Schlenk flask and heated to 200 °C for 15 minutes under vacuum. Upon cooling to ambient temperature 5-fluoro-2-methoxybenzonitrile (0.756 g, 5.00 mmol), a Teflon-coated magnetic stir bar and anhydrous DMSO (9 ml) were added to the flask and the resulting mixture stirred at 155 °C for 6 h. The reaction mixture was cooled to room temperature, water was added and the resulting layer extracted three times with ethyl acetate. The combined organic layers were washed with water and brine, dried with sodium sulfate, filtered and concentrated under reduced pressure to give a colorless solid. The analytical data of the product 5-fluoro-2-hydroxybenzonitrile (0.352 g, 25%) obtained after purification *via* flash column chromatography was in accordance with that found in the literature.[38]

7-Hydroxy-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbonitrile

Following general procedure A 5.53 g (30.7 mmol) dihydro-2,3-formyl-7-hydroxy-6-benzodioxane-1,4, 4.5 ml (4.7 g, 63 mmol) nitroethane and 5.17 g (63.0 mmol) sodium acetate were refluxed in 6.3 ml glacial acetic acid. After concentrating the organic layers under reduced pressure the residue was suspended in dichloromethane, filtered and washed with dichloromethane to afford the title compound as a faintly red solid (2.84 g, 52%, mp 210 °C (decomp.)). **^{1}H NMR** (d_6-

acetone): δ 7.01 (s, 1H), 6.49 (s, 1H), 4.33-4.30 (m, 2H), 4.23-4.21 (m, 2H). **^{13}C NMR** (d_6-acetone): δ 155.8, 150.0, 138.4, 121.2, 117.3, 105.4, 93.0, 66.1, 65.0. **IR** (neat, cm^{-1}): 3312, 3082, 2951, 2219, 1595, 1513, 1432, 1291, 1193, 1061, 882, 843. **HRMS** (ESI) *m/z* calculated for $C_9H_8NO_3^+$ ($M + H^+$) 178.0504, found 178.0506.

6-Hydroxybenzo[*d*][1,3]dioxole-5-carbonitrile

Following general procedure A 1.89 g (11.4 mmol) 6-hydroxybenzo[*d*][1,3]dioxole-5-carbaldehyde, 1.7 ml (1.8 g, 24 mmol) nitroethane and 1.94 g (23.6 mmol) sodium acetate were refluxed in 4 ml glacial acetic acid. After concentrating the organic layers under reduced pressure the residue was purified *via* flash column chromatography using mixtures of diethylether and n-pentane as eluent to afford the title compound as an orange-colored solid (0.666 g, 36%, mp 216 °C (decomp.)). **^{1}H NMR** (d_6-acetone): δ 6.98 (s, 1H), 6.59 (s, 1H), 6.07 (s, 2H). **^{13}C NMR** (d_6-acetone): δ 158.2, 153.7, 142.1, 117.5, 110.8, 103.5, 98.8, 91.3. **IR** (neat, cm^{-1}): 3237, 2917, 1627, 1493, 1439, 1311, 1182, 1032, 928, 738. **HRMS** (ESI) *m/z* calculated for $C_8H_6NO_3^+$ ($M + H^+$) 164.0348, found 164.0350.

4.6.2.2 Preparation of Dihydrooxazines

General Procedure B: Synthesis of Dihydrooxazines from the corresponding 2-Hydroxybenzonitriles

Dihydrooxazines were synthesized using a modified published procedure.[39] A round-bottom flask was charged with the appropriate 2-hydroxybenzonitrile (10.0 mmol), zinc chloride (1.0 mmol, 10 mol %) and the appropriate aminoalcohol (if solid,

15.8 mmol) in a glove box. Upon removal of the flask from the glove box chlorobenzene (30 ml) and the appropriate aminoalcohol (if liquid, 15.8 mmol) were added and the resulting mixture refluxed for 24-36 h. The reaction mixture was then cooled to ambient temperature and volatiles removed *in vacuo*. The resulting residue was dissolved in ethyl acetate and washed three times with water and the combined aqueous layers reextracted with ethyl acetate. The combined organic layers were washed with brine, dried with sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude dihydrooxazine was then purified *via* flash column chromatography.

2-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-4-fluorophenol (1b)

Following general procedure B using 155 mg (1.13 mmol) 5-fluoro-2-hydroxy-benzonitrile, 16 mg (0.12 mmol, 10 mol %) $ZnCl_2$, 0.16 ml (0.16 g, 2.1 mmol) 3-aminopropan-1-ol and 4.5 ml chlorobenzene afforded the title compound as a colorless solid (172 mg, 78%, mp 34-35 °C). **^{1}H NMR** ($CDCl_3$): δ 13.81 (s, 1H), 7.32 (dd, J = 9.5 Hz, J = 3.2 Hz, 1H), 6.99 (ddd, J = 8.9 Hz, J = 8.1 Hz, J = 3.2 Hz, 1H), 6.84 (dd, J = 9.0 Hz, J = 4.7 Hz, 1H), 4.37 (t, J = 5.5 Hz, 2H), 3.58 (t, J = 5.9 Hz, 2H), 2.04-1.99 (m, 2H). **^{13}C NMR** ($CDCl_3$): δ 158.7 (d, J = 2.6 Hz), 157.1 (d, J = 1.6 Hz), 154.9 (d, J = 234.8 Hz), 119.5 (d, J = 23.4 Hz), 118.1 (d, J = 7.4 Hz), 114.8 (d, J = 7.8 Hz), 112.6 (d, J = 24.5 Hz), 65.7, 41.1, 21.7. **^{19}F NMR** ($CDCl_3$): δ -126.43. **IR** (neat, cm^{-1}): 2938, 2870, 1640, 1614, 1497, 1359, 1259, 1181, 1090, 965, 770. **HRMS** (ESI) *m/z* calculated for $C_{10}H_{11}FNO_2^+$ ($M + H^+$) 196.0774, found 196.0774.

2-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-4-methylphenol (1c)

Following general procedure B using 450 mg (3.38 mmol) 2-hydroxy-5-methyl-benzonitrile, 44 mg (0.32 mmol, 10 mol %) $ZnCl_2$, 0.41 ml (0.41 g, 5.4 mmol) 3-aminopropan-1-ol and 10 ml chlorobenzene afforded the title compound as a yellow solid (500 mg, 77%, mp 35-37 °C). **^{1}H NMR** ($CDCl_3$): δ 13.90 (s, 1H), 7.45 (d, J = 2.5 Hz, 1H), 7.09, (dd, J = 8.4 Hz, J = 2.5 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 4.36 (t, J = 5.5 Hz, 2H), 3.57 (t, J = 5.9 Hz, 2H), 2.24 (s, 3H), 2.03-1.97 (m, 2H). **^{13}C NMR** ($CDCl_3$): δ 159.4, 158.8, 133.3, 126.8, 126.8, 117.0, 114.3, 65.5, 41.1, 21.8, 20.7. **IR** (neat, cm^{-1}): 2942, 1638, 1493, 1357, 1257, 1194, 1100, 844, 764. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{14}NO_2^+$ ($M + H^+$) 192.1025, found 192.1026.

2-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-4-methoxyphenol (1d)

Following general procedure B using 370 mg (2.48 mmol) 2-hydroxy-5-methoxy-benzonitrile, 30 mg (0.22 mmol, 9 mol %) $ZnCl_2$, 0.30 ml (0.30 g, 3.9 mmol) 3-aminopropan-1-ol and 7.5 ml chlorobenzene afforded the title compound as an off-white solid (424 mg, 83%, mp 70-71 °C). **^{1}H NMR** ($CDCl_3$): δ 13.62 (s, 1H), 7.16 (d, J = 3.1 Hz, 1H), 6.90 (dd, J = 8.9 Hz, J = 3.1 Hz, 1H), 6.83 (d, J = 8.9 Hz, 1H), 4.37 (t, J = 5.4 Hz, 2H), 3.74 (s, 3H), 3.58 (t, J = 5.9 Hz, 2H), 2.04-1.98 (m, 2H). **^{13}C NMR** ($CDCl_3$): δ 159.1, 155.3, 151.4, 120.1, 118.0, 114.4, 110.3, 65.6, 56.1, 41.1, 21.8. **IR** (neat, cm^{-1}): 2932, 1602, 1208, 1360, 1280, 1180, 1032, 817, 766. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{14}NO_3^+$ ($M + H^+$) 208.0974, found 208.0979.

3-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-[1,1'-biphenyl]-4-ol (1e)

Following general procedure B using 300 mg (1.54 mmol) 4-hydroxy-[1,1'-biphenyl]-3-carbonitrile, 21 mg (0.15 mmol, 10 mol %) $ZnCl_2$, 0.20 ml (0.20 g, 2.6 mmol) 3-aminopropan-1-ol and 5 ml chlorobenzene afforded the title compound as an off-white solid (294 mg, 75%, mp 84-86 °C). **^{1}H NMR** ($CDCl_3$): δ 14.26 (s, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.56-7.53 (m, 3H), 7.41-7.37 (m, 2H), 7.27 (t, J = 7.4 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 4.41 (t, J = 5.4 Hz, 2H), 3.61 (t, J = 5.9 Hz, 2H), 2.07-2.01 (m, 2H). **^{13}C NMR** ($CDCl_3$): δ 160.8, 159.6, 141.0, 131.3, 130.9, 128.9, 126.8, 126.7, 125.4, 117.8, 114.8, 65.6, 41.1, 21.8. **IR** (neat, cm^{-1}): 2950, 1634, 1591, 1479, 1359, 1238, 1101, 832, 761, 689. **HRMS** (ESI) *m/z* calculated for $C_{16}H_{16}NO_2^+$ ($M + H^+$) 254.1181, found 254.1179.

2-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-5-methylphenol (1f)

Following general procedure B using 192 mg of crude 2-hydroxy-4-methylbenzonitrile, 38 mg (0.28 mmol) $ZnCl_2$, 0.18 ml (0.18 g, 2.4 mmol) 3-aminopropan-1-ol and 6.5 ml chlorobenzene afforded the title compound as a colorless solid (128 mg, 19% (over two steps), mp 58-59 °C). **^{1}H NMR** ($CDCl_3$): δ 14.12 (s, 1H), 7.51 (d, J = 8.1 Hz, 1H), 6.72 (s, 1H), 6.58 (d, J = 8.1 Hz, 1H), 4.36 (t, J = 5.4 Hz, 2H), 3.57 (t, J = 5.9 Hz, 2H), 2.29 (s, 3H), 2.03-1.97 (m, 2H). **^{13}C NMR** ($CDCl_3$): δ 161.1, 159.5, 143.2, 126.7, 119.0, 117.7, 112.2, 65.4, 41.0, 21.9, 21.8. **IR** (neat, cm^{-1}): 2939, 2904, 1635, 1610, 1514, 1359, 1242, 1151, 913, 811, 686. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{14}NO_2^+$ ($M + H^+$) 192.1025, found 192.1024.

2-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-5-methoxyphenol (1g)

Following general procedure B using 315 mg (2.07 mmol) 2-hydroxy-4-methoxy-benzonitrile, 29 mg (2.1 mmol, 10 mol %) $ZnCl_2$, 0.26 ml (0.26 g, 3.4 mmol) 3-aminopropan-1-ol and 6 ml chlorobenzene afforded the title compound as a colorless solid (157 mg, 37%, mp 62-64 °C). **^{1}H NMR** ($CDCl_3$): δ 14.61 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 6.41 (d, J = 2.6 Hz, 1H), 6.32 (dd, J = 8.8 Hz, J = 2.6 Hz, 1H), 4.35 (t, J = 5.5 Hz, 2H), 3.77 (s, 3H), 3.55 (t, J = 6.0 Hz, 2H), 2.03-1.97 (m, 2H). **^{13}C NMR** ($CDCl_3$): δ 163.5, 163.3, 159.8, 128.0, 107.8, 105.5, 101.2, 65.5, 55.4, 40.7, 21.9. **IR** (neat, cm^{-1}): 2940, 2859, 1607, 1443, 1359, 1263, 1141, 1035, 913, 947, 805. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{14}NO_3^+$ ($M + H^+$) 208.0974, found 208.0976.

2-Bromo-6-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (1h)

Following general procedure B using 596 mg (3.01 mmol) 3-bromo-2-hydroxy-benzonitrile, 42 mg (0.31 mmol, 10 mol %) $ZnCl_2$, 0.38 ml (0.38 g, 5.0 mmol) 3-aminopropan-1-ol and 10 ml chlorobenzene afforded the title compound as a yellow solid (391 mg, 51%, mp 100-101 °C). **^{1}H NMR** ($CDCl_3$): δ 15.58 (s, 1H), 7.58 (dd, J = 8.0 Hz, J = 1.7 Hz, 1H), 7.53 (dd, J = 7.8 Hz, J = 1.7 Hz, 1H), 6.61 (t, J = 7.9 Hz, 1H), 4.39 (t, J = 5.5 Hz, 2H), 3.58 (t, J = 6.0 Hz, 2H), 2.06-2.00 (m, 2H). **^{13}C NMR** ($CDCl_3$): δ 160.0, 159.9, 136.0, 126.1, 118.0, 115.1, 111.7, 65.9, 40.6, 21.5. **IR** (neat, cm^{-1}): 2963, 1635, 1590, 1435, 1381, 1265, 1152, 1034, 952, 833, 753. **HRMS** (ESI) *m/z* calculated for $C_{10}H_{11}BrNO_2^+$ ($M + H^+$) 255.9973, found 255.9974.

6-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)benzo[*d*][1,3]dioxol-5-ol (1i)

Following general procedure B using 0.576 mg (3.53 mmol) 6-hydroxybenzo[*d*][1,3]dioxole-5-carbonitrile, 48 mg (0.35 mmol) $ZnCl_2$, 0.43 ml (0.42 g, 5.7 mmol) 3-aminopropan-1-ol and 11 ml chlorobenzene afforded the title compound as a faintly yellow solid (0.461 mg, 59%, mp 94-95 °C). **^{1}H NMR** ($CDCl_3$): δ 14.65 (br s, 1H), 7.04 (s, 1H), 6.42 (s, 1H), 5.87 (s, 2H), 4.35 (t, J = 5.3 Hz, 2H), 3.55 (t, J = 5.9 Hz, 2H), 2.04-1.98 (m, 2H). **^{13}C NMR** ($CDCl_3$): δ 159.9, 159.6, 151.1, 139.4, 105.9, 104.9, 101.2, 98.7, 65.5, 40.5, 21.8. **IR** (neat, cm^{-1}): 3063, 2890, 1630, 1452, 1430, 1391, 1248, 1128, 1039, 837, 691. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{12}NO_4^+$ ($M + H^+$) 222.0766, found 222.0767.

7-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)-2,3-dihydrobenzo[*b*][1,4]dioxin-6-ol (1j)

Following general procedure B using 451 mg (2.54 mmol) 7-hydroxy-2,3-dihydrobenzo[*b*][1,4]dioxine-6-carbonitrile, 35 mg (0.26 mmol, 10 mol %) $ZnCl_2$, 0.33 ml (0.33 g, 4.3 mmol) 3-aminopropan-1-ol and 8.5 ml chlorobenzene afforded the title compound as a faintly orange-colored colorless solid (236 mg, 40%, mp 105-108 °C). **^{1}H NMR** ($CDCl_3$): δ 13.82 (s, 1H), 7.14 (s, 1H), 6.40 (s, 1H), 4.34 (t. J = 5.5 Hz, 2H), 4.25-4.22 (m, 2H), 4.18-4.15 (m, 2H), 3.55 (t, J = 5.9 Hz, 2H), 2.02-1.97 (m, 2H). **^{13}C NMR** ($CDCl_3$): δ 159.1, 156.3, 147.2, 135.6, 114.7, 108.2, 104.7, 65.5, 65.0, 64.2, 40.9, 21.9. **IR** (neat, cm^{-1}): 2976, 2864, 1640, 1593, 1504, 1359, 1302, 1245, 1065, 894, 854. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{14}NO_4^+$ ($M + H^+$) 236.0923, found 236.0920.

3-(5,6-Dihydro-4*H*-1,3-oxazin-2-yl)naphthalen-2-ol (1k)

Following general procedure B using 678 mg (4.01 mmol) 3-hydroxy-2-naphthonitrile, 55 mg (0.40 mmol, 10 mol %) $ZnCl_2$, 0.5 ml (0.49 g, 6.6 mmol) 3-aminopropan-1-ol and 12 ml chlorobenzene afforded the title compound as a colorless solid (715 mg, 79%, mp 74-76 °C). **^{1}H NMR** ($CDCl_3$): δ 13.81 (s, 1H), 8.30 (s, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.47 (ddd, J = 8.1 Hz, J = 6.9 Hz, J = 1.2 Hz, 1H), 7.33-7.29 (m, 2H), 4.45 (t, J = 5.5 Hz, 2H), 3.66 (t, J = 5.9 Hz, 2H), 2.10-2.04 (m, 2H). **^{13}C NMR** ($CDCl_3$): δ 159.0, 157.0, 136.4, 126.9, 128.2, 127.8, 126.8, 126.1, 123.1, 117.0, 110.9, 65.6, 41.3, 21.7. **IR** (neat, cm^{-1}): 2969, 1644, 1516, 1470, 1354, 1288, 1122, 904, 841, 756, 622. **HRMS** (ESI) *m/z* calculated for $C_{14}H_{14}NO_2^+$ ($M + H^+$) 228.1025, found 228.1024.

2-(4-Methyl-5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (1l)

Following general procedure B using 456 mg (3.83 mmol) 2-hydroxybenzonitrile, 53 mg (0.39 mmol, 10 mol %) $ZnCl_2$, 550 mg (6.17 mmol) 3-aminobutan-1-ol and 10 ml chlorobenzene afforded the title compound as a yellow solid (500 mg, 77%, mp 35-37 °C). **^{1}H NMR** ($CDCl_3$): δ 14.38 (s, 1H), 7.65 (dd, J = 7.9 Hz, J = 1.7 Hz, 1H), 7.27 (ddd, J = 8.3 Hz, J = 7.2 Hz, J = 1.7 Hz, 1H), 6.90 (dd, J = 8.3 Hz, J = 1.2 Hz, J = 0.4 Hz, 1H), 6.77 (ddd, J = 7.2 Hz, J = 7.9 Hz, J = 1.2 Hz, 1H), 4.42 (dt, J = 11.0 Hz, J = 4.3 Hz, 1H), 4.30 (td, J = 10.4 Hz, J = 3.2 Hz, 1H), 3.73-3.64 (m, 1H), 2.09-2.02 (m, 1H), 1.75-1.66 (m, 1H), 1.32 (d, J = 6.8 Hz, 3H). **^{13}C NMR** ($CDCl_3$): δ 161.3, 158.5, 132.6, 127.0, 117.8, 117.4, 114.6, 64.6, 46.4, 29.3, 23.2. **IR** (neat, cm^{-1}): 2969, 2886,

1630, 1497, 1358, 1265, 1193, 1106, 759, 690. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{14}NO_2^+$ ($M + H^+$) 192.1025, found 192.1023.

2-(4-Phenyl-5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (1m)

Following general procedure B using 397 mg (3.33 mmol) 2-hydroxybenzonitrile, 45 mg (0.33 mmol, 10 mol %) $ZnCl_2$, 756 mg (5.00 mmol) 3-amino-3-phenylpropan-1-ol and 10 ml chlorobenzene afforded the title compound as a colorless solid (720 mg, 85%, mp 60-61 °C). **^{1}H NMR** ($CDCl_3$): δ 14.17 (br s, 1H), 7.75 (dd, J = 7.9 Hz, J = 1.7 Hz, 1H), 7.38-7.24 (m, 6H), 6.95 (d, J = 8.3 Hz, 1H), 6.83 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 4.83 (dd, J = 8.1 Hz, J = 5.1 Hz, 1H), 4.46-4.36 (m, 2H), 2.38-2.31 (m, 1H), 2.05-1.96 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 161.3, 160.0, 143.2, 132.9, 128.8, 127.4, 127.3, 126.5, 118.0, 117.5, 114.6, 64.3, 54.3, 30.4. **IR** (neat, cm^{-1}): 2969, 1630, 1603, 1494, 1454, 1257, 771, 702, 572. **HRMS** (ESI) *m/z* calculated for $C_{16}H_{16}NO_2^+$ ($M + H^+$) 254.1181, found 254.1179.

2-(4,4-Dimethyl-5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (1n)

Following general procedure B using 834 mg (7.00 mmol) 2-hydroxybenzonitrile, 100 mg (0.33 mmol, 10 mol %) $ZnCl_2$, 1.18 g (11.4 mmol) 3-amino-3-methylbutan-1-ol and 21 ml chlorobenzene afforded the title compound as an off-white solid (1.30 g, 91%, mp 31-32 °C). **^{1}H NMR** ($CDCl_3$): δ 14.44 (s, 1H), 7.65 (dd, J = 7.9 Hz, J = 1.8 Hz, 1H), 7.27 (ddd, J = 9.0 Hz, J = 7.2 Hz, J = 1.8 Hz, 1H), 6.90 (dd, J = 8.3 Hz, J = 1.2 Hz, 1H), 6.77 (ddd, J = 9.0 Hz, J = 8.3 Hz, J = 1.2 Hz, 1H), 4.35 (t, J = 5.7 Hz, 2H), 1.86 (t, J = 5.7 Hz, 2H), 1.32 (s, 6H). **^{13}C NMR** ($CDCl_3$): δ 161.2, 157.5, 132.5,

127.1, 117.8, 117.3, 114.7, 62.7, 48.7, 34.2, 30.1. **IR** (neat, cm^{-1}): 2961, 2919, 1625, 1599, 1497, 1384, 1326, 1245, 1088, 854, 751. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{16}NO_2^+$ ($M + H^+$) 206.1181, found 206.1181.

2-(5-Methyl-5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (1o)

Following general procedure B using 271 mg (2.28 mmol) 2-hydroxybenzonitrile, 33 mg (0.33 mmol, 11 mol %) $ZnCl_2$, 341 mg (3.83 mmol) 3-amino-2-methylpropan-1-ol and 7 ml chlorobenzene afforded the title compound as a colorless solid (349 mg, 80%, mp 66-67 °C). **^{1}H NMR** ($CDCl_3$): δ 14.20 (s, 1H), 7.66 (dd, J = 8.0 Hz, J = 1.7 Hz, 1H), 7.28 (ddd, J = 8.3 Hz, J = 7.2 Hz, J = 1.8 Hz, 1H), 6.91 (ddd, J = 8.3 Hz, J = 1.2 Hz, J = 0.4 Hz, 1H), 6.77 (ddd, J = 7.9 Hz, J = 7.2 Hz, J = 1.2 Hz, 1H), 4.34 (ddd, J = 10.6 Hz, J = 4.1 Hz, J = 2.5 Hz, 1H), 3.86 (t, J = 10.3 Hz, 1H), 3.63 (ddd, J = 16.2 Hz, J = 5.0 Hz, J = 2.5 Hz, 1H), 3.13 (dd, J = 16.2 Hz, J = 9.4 Hz, 1H), 2.19-2.06 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H). **^{13}C NMR** ($CDCl_3$): δ 161.1, 159.1, 132.6, 127.0, 117.8, 117.3, 114.6, 70.7, 48.4, 26.2, 15.0. **IR** (neat, cm^{-1}): 2963, 2926, 1637, 1603, 1500, 1455, 1345, 1206, 932, 757, 688. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{14}NO_2^+$ ($M + H^+$) 192.1025, found 192.1024.

2-(3,4-Dimethoxyphenyl)-5,6-dihydro-4H-1,3-oxazine (1q)

Following general procedure B using 1.63 g (10.0 mmol) 3,4-dimethoxybenzonitrile, 10 mg (0.70 mmol, 7 mol %) $ZnCl_2$, 1.18 mg (15.7 mmol) 3-aminopropan-1-ol and 30 ml chlorobenzene afforded the title compound as a colorless solid (987 mg, 45%). **^{1}H NMR** (400 MHz, C_6D_6): δ 7.96 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 8.4, 2.0

Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 3.78 (t, *J* = 5.4 Hz, 2H), 3.47 (s, 3H), 3.41 (t, *J* = 5.9 Hz, 2H), 3.32 (s, 3H), 1.33 (p, *J* = 5.8 Hz, 2H).

4.6.2.3 Hydroformylation of Dihydrooxazines

General Procedure C: Hydroformylation of Dihydrooxazines

In a glove box, vials equipped with Teflon-coated magnetic stir bars were charged with $Co_2(CO)_8$, the appropriate dihydrooxazine and toluene. The vials were then placed in a custom-made 6-well high-pressure reactor[40] which was subsequently closed, taken out of the glove box and pressured with carbon monoxide (500 psi partial pressure) and hydrogen (500 psi partial pressure). The reactor was then sealed and the reaction mixtures were stirred for 20 h at 80 °C. The reactor was then cooled to ambient temperature and carefully vented in a well-ventilated hood. The crude reaction mixtures were concentrated *in vacuo* and then purified by flash column chromatography.

3,3a-Dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2a)

Following general procedure C using 88.6 mg (0.500 mmol) 2-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (**1a**), 7.0 mg (0.020 mmol, 4.0 mol %) $Co_2(CO)_8$ and 2 ml toluene afforded the title compound as a colorless solid (77.0 mg, 81%, mp 68-70 °C). The analytical data was in accordance with that in the literature.[41]

7-Fluoro-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2b)

Following general procedure C using 79.0 mg (0.405 mmol) 2-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)-4-fluorophenol (**1b**), 5.5 mg (0.016 mmol, 4.0 mol %) $Co_2(CO)_8$ and 1.6 ml toluene afforded the title compound as a colorless solid (54.7 mg, 65%, mp 77-80 °C). **^{1}H NMR** ($CDCl_3$): δ 7.56 (dd, J = 8.2 Hz, J = 3.1 Hz, 1H), 7.09 (ddd, J = 8.9 Hz, J = 8.1 Hz, J = 3.2 Hz, 1H), 6.90 (dd, J = 8.9 Hz, J = 4.2 Hz, 1H), 5.40 (t, J = 5.8 Hz, 1H), 3.80 (dt, J = 11.6 Hz, J = 7.3 Hz, 1H), 3.58 (ddd, J = 11.8 Hz, J = 8.0 Hz, J = 5.0 Hz, 1H), 2.44-2.37 (m, 1H), 2.26-2.17 (m, 1H), 2.13-2.04 (m, 1H), 1.97-1.86 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 160.2, 158.2 (d, J = 242.0 Hz), 153.5 (d, J = 2.0 Hz), 121.0, 120.9 (d, J = 24.1 Hz), 118.1 (d, J = 7.6 Hz), 114.0 (d, J = 24.5 Hz), 88.9, 44.6, 32.0, 21.5. **^{19}F NMR** ($CDCl_3$): δ -119.88. **IR** (neat, cm^{-1}): 3039, 2980, 2883, 1667, 1590, 1482, 1349, 1256, 1078, 963, 767. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{11}FNO_2^+$ ($M + H^+$) 208.0774, found 208.0772.

7-Methyl-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2c)

Following general procedure C using 77.0 mg (0.403 mmol) 2-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)-4-methylphenol (**1c**), 5.5 mg (0.016 mmol, 4.0 mol %) $Co_2(CO)_8$ and 3.3 ml toluene afforded the title compound as an off-white solid (60.0 mg, 73%, mp 95-97 °C). **^{1}H NMR** ($CDCl_3$): δ 7.68 (d, J = 2.3 Hz, 1H), 7.18 (dd, J = 8.3 Hz, J = 2.4 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 5.41 (t, J = 5.8 Hz, 1H), 3.80 (dt, J = 11.6 Hz, J = 7.4 Hz, 1H), 3.57 (ddd, J = 11.7 Hz, J = 8.0 Hz, J = 5.0 Hz, 1H), 2.43-2.35 (m, 1H), 2.29 (s, 3H), 2.24-2.15 (m, 1H), 2.13-2.01 (m, 1H), 1.93-1.84 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 161.3, 155.3, 134.7, 132.3, 128.0, 120.0, 116.3, 88.6, 44.4, 32.1, 21.5,

20.6. **IR** (neat, cm^{-1}): 3047, 2942, 2891, 1658, 1611, 1434, 1338, 1182, 1074, 827. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{14}NO_2^+$ ($M + H^+$) 204.1025, found 204.1023.

7-Methoxy-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2d)

Following general procedure C using 84.0 mg (0.405 mmol) 2-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)-4-methoxyphenol (**1d**), 5.5 mg (0.016 mmol, 4.0 mol %) $Co_2(CO)_8$ and 3.3 ml toluene afforded the title compound as a colorless solid (77.1 mg, 87%, mp 90-92 °C). **^{1}H NMR** ($CDCl_3$): δ 7.37 (d, J = 3.1 Hz, 1H), 6.96 (dd, J = 8.9 Hz, J = 3.1 Hz, 1H), 6.86 (d, J = 8.9 Hz, 1H), 5.42 (t, J = 5.8 Hz, 1H), 3.80 (dt, J = 11.6 Hz, J = 7.4 Hz, 1H), 3.79 (s, 3H), 3.59 (ddd, J = 11.7 Hz, J = 8.0 Hz, J = 4.9 Hz, 1H), 2.43-2.35 (m, 1H), 2.25-2.16 (m, 1H), 2.13-2.04 (m, 1H), 1.96-1.84 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 160.9, 155.0, 151.3, 121.5, 120.0, 117.5, 110.0, 88.5, 55.8, 44.3, 31.9, 21.4. **IR** (neat, cm^{-1}): 2896, 2838, 1663, 1619, 1484, 1272, 1179, 1078, 905, 817, 756. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{14}NO_3^+$ ($M + H^+$) 220.0974, found 220.0973.

7-Phenyl-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2e)

Following general procedure C using 126 mg (0.497 mmol) 3-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)-[1,1'-biphenyl]-4-ol (**1e**), 7.0 mg (0.020 mmol, 4.0 mol %) $Co_2(CO)_8$ and 4.0 ml toluene afforded the title compound as a colorless solid (95.2 mg, 72%, mp 135-138 °C). **^{1}H NMR** ($CDCl_3$): δ 8.15 (d, J = 2.3 Hz, 1H), 7.64 (dd, J = 8.5 Hz, J = 2.4 Hz, 1H), 7.58-7.56 (m, 2H), 7.43-7.39 (m, 2H), 7.31 (t, J = 7.3 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 5.49 (t, J = 5.8 Hz, 1H), 3.84 (dt, J = 11.6 Hz, J = 7.3 Hz, 1H), 3.62 (ddd, J = 11.6 Hz, J = 8.0 Hz, J = 5.0 Hz, 1H), 2.46-2.39 (m, 1H), 2.29-2.20 (m, 1H),

2.13-2.05 (m, 1H), 1.98-1.87 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 161.0, 156.8, 139.9, 136.0, 132.5, 129.0, 127.5, 127.0, 126.4, 120.1, 117.1, 88.8, 44.5, 32.1, 21.5. **IR** (neat, cm^{-1}): 2996, 2895, 1674, 1614, 1439, 1342, 1063, 832, 764, 699. **HRMS** (ESI) *m/z* calculated for $C_{17}H_{16}NO_2^+$ ($M + H^+$) 266.1181, found 266.1181.

6-Methyl-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2f)

Following general procedure C using 77.0 mg (0.403 mmol) 2-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)-5-methylphenol (**1f**), 5.5 mg (0.016 mmol, 4.0 mol %) $Co_2(CO)_8$ and 3.3 ml toluene afforded the title compound as a colorless solid (58.9 mg, 72%, mp 81-84 °C). **^{1}H NMR** ($CDCl_3$): δ 7.77 (d, J = 7.9 Hz, 1H), 6.9 (d, J = 7.8 Hz, 1H), 6.72 (s, 1H), 5.42 (t, J = 5.8 Hz, 1H), 3.79 (dt, J = 11.5 Hz, J = 7.3 Hz, 1H), 3.57 (ddd, J = 11.6 Hz, J = 8.0 Hz, J = 5.1 Hz, 1H), 2.43-2.35 (m, 1H), 2.32 (s, 3H), 2.24-2.15 (m, 1H), 2.11-2.02 (m, 1H), 1.95-1.84 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 161.3, 157.5, 145.0, 127.9, 123.8, 117.3, 116.9, 88.6, 44.4, 32.1, 21.9, 21.5. **IR** (neat, cm^{-1}): 2980, 2891, 1657, 1617, 1428, 1347, 1112, 1074, 935, 772. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{14}NO_2^+$ ($M + H^+$) 204.1025, found 204.1024.

6-Methoxy-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2g)

Following general procedure C using 83.0 mg (0.401 mmol) 2-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)-5-methoxyphenol (**1g**), 5.5 mg (0.016 mmol, 4.0 mol %) $Co_2(CO)_8$ and 3.3 ml toluene afforded the title compound as a colorless solid (64.2 mg, 73%, mp 119-122 °C). **^{1}H NMR** ($CDCl_3$): δ 7.81 (d, J = 8.7 Hz, 1H), 6.61 (dd, J = 8.7 Hz, J = 2.4 Hz, 1H), 6.41 (d, J = 2.4 Hz, 1H), 5.45 (t, J = 5.8 Hz, 1H), 3.81-3.75 (m, 1H), 3.78

(s, 3H), 3.59-3.53 (m, 1H), 2.43-2.35 (m, 1H), 2.24-2.16 (m, 1H), 2.11-2.02 (m, 1H), 1.95-1.84 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 164.3, 161.2, 159.2, 129.5, 112.9, 109.7, 101.0, 88.9, 55.7, 44.4, 21.1, 21.6. **IR** (neat, cm^{-1}): 2971, 2895, 1665, 1607, 1438, 1349, 1268, 1102, 1023, 855, 769. **HRMS** (ESI) *m/z* calculated $C_{12}H_{14}NO_3^+$ ($M + H^+$) 220.0974, found 220.0974.

5-Bromo-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2h)

Following general procedure C using 128 mg (0.500 mmol) 2-bromo-6-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (**1h**), 7.0 mg (0.02 mmol, 4.0 mol %) $Co_2(CO)_8$ and 2 ml toluene afforded the title compound as a colorless solid (106 mg, 79%, mp 85-88 °C). **^{1}H NMR** ($CDCl_3$): δ 7.85 (dd, J = 7.7 Hz, J = 1.6 Hz, 1H), 7.61 (dd, J = 7.9 Hz, J = 1.6 Hz, 1H), 6.96 (t, J = 7.8 Hz, 1H), 5.52 (t, J = 5.7 Hz, 1H), 3.83 (dt, J = 11.6 Hz, J = 7.3 Hz, 1H), 3.59 (ddd, J = 11.7 Hz, J = 8.0 Hz, J = 5.3 Hz, 1H), 2.51-2.43 (m, 1H), 2.39-2.30 (m, 1H), 2.17-2.07 (m, 1H), 2.01-1.88 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 160.3, 154.4, 137.3, 127.4, 123.6, 121.4, 110.4, 89.2, 44.7, 32.1, 21.6. **IR** (neat, cm^{-1}): 2982, 2887, 1668, 1597, 1429, 1336, 1067, 854, 757, 684. **HRMS** (ESI) *m/z* calculated for $C_{11}H_{11}NO_2Br^+$ ($M + H^+$) 267.9973, found 267.9974.

7,8-Dihydro-5a*H*-[1,3]dioxolo[4',5':4,5]benzo[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-10-(6*H*)-one (2i)

Following general procedure C using 87.5 mg (0.396 mmol) 6-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)benzo[*d*][1,3]dioxol-5-ol (**1i**), 5.5 mg (0.016 mmol, 4.0 mol %) $Co_2(CO)_8$ and 3.3 ml toluene afforded the title compound as a colorless solid (70.6

mg, 76%, mp 162-164 °C). **^{1}H NMR** ($CDCl_3$): δ 7.25 (s, 1H), 6.39 (s, 1H), 5.94-5.93 (m, 2H), 5.38 (t, J = 5.7 Hz, 1H), 3.75 (dt, J = 11.4 Hz, J = 7.2 Hz, 1H), 3.53 (ddd, J = 11.4 Hz, J = 7.9 Hz, J = 5.2 Hz, 1H), 2.39-2.31 (m, 1H), 2.21-2.12 (m, 1H), 2.09-2.00 (m, 1H), 1.93-18.2 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 161.0, 154.2, 152.1, 143.5, 112.8, 106.2, 102.0, 98.0, 88.9, 44.4, 32.0, 21.7. **IR** (neat, cm^{-1}): 2979, 2914, 1650, 1455, 1251, 1135, 1031, 932, 769. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{12}NO_4^+$ ($M + H^+$) 234.0766, found 234.0767. The analytical data was in accordance with that found in the literature.[42]

6a,7,8,9-Tetrahydro-2*H*-[1,4]dioxino[2',3':4,5]benzo[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-11(3H)-one (2j)

Following general procedure C using 93.5 mg (0.397 mmol) 7-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)-2,3-dihydrobenzo[*b*][1,4]dioxin-6-ol (**1j**), 5.5 mg (0.016 mmol, 4.0 mol %) $Co_2(CO)_8$ and 3.3 ml toluene afforded the title compound as a colorless solid (70.1 mg, 71%, mp 155-158 °C). **^{1}H NMR** ($CDCl_3$): δ 7.37 (s, 1H), 6.41 (s, 1H), 5.38 (t, J = 5.8 Hz, 1H), 4.25-4.23 (m, 2H), 4.19-4.17 (m, 2H), 3.76 (dt, J = 11.5 Hz, J = 7.3 Hz, 1H), 3.55 (ddd, J = 11.5 Hz, J = 8.0 Hz, J = 5.0 Hz, 1H), 2.40-2.32 (m, 1H), 2.21-2.12 (m, 1H), 2.08-2.00 (m, 1H), 1.93-1.82 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 160.9, 152.3, 148.2, 140.0, 115.9, 113.4, 104.7, 88.8, 65.0, 64.0, 44.4, 32.1, 21.6. **IR** (neat, cm^{-1}): 2986, 2879, 1652, 1623, 1448, 1299, 1149, 1058, 897, 760. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{14}NO_4^+$ ($M + H^+$) 248.0923, found 248.0925. The analytical data was in accordance with that found in the literature.[19]

3,3a-Dihydro-1*H*-Naphtho[2,3-*e*]pyrrolo[2,1-*b*][1,3]oxazin-11(2*H*)-one (2k)

Following general procedure C using 94.0 mg (0.414 mmol) 3-(5,6-dihydro-4*H*-1,3-oxazin-2-yl)naphthalen-2-ol (**1k**), 5.5 mg (0.016 mmol, 4.0 mol %) $Co_2(CO)_8$ and 3.3 ml toluene afforded the title compound as a colorless solid (79.5 mg, 80%, mp 118-121 °C). **^{1}H NMR** ($CDCl_3$): δ 8.48 (s, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.48 (dd, J = 8.2 Hz, J = 7.0 Hz, 1H), 7.37 (dd, J = 8.2 Hz, J = 7.0 Hz, 1H), 7.30 (s, 1H), 5.48 (t, J = 5.9 Hz, 1H), 3.88-3.83 (m, 1H), 3.68-3.62 (m, 1H), 2.47-2.40 (m, 1H), 2.28-2.19 (m, 1H), 2.14-2.06 (m, 1H), 1.97-1.88 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 161.1, 153.6, 136.4, 129.53, 129.49, 129.47, 128.6, 127.0, 125.2, 120.2, 112.2, 88.7, 44.6, 32.2, 21.3. **IR** (neat, cm^{-1}): 2958, 2892, 1662, 1630, 1434, 1337, 1101, 1071, 876, 749, 639. **HRMS** (ESI) *m/z* calculated for $C_{15}H_{14}NO_2^+$ ($M + H^+$) 240.1025, found 240.1024.

1-Methyl-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2l)

Following general procedure C using 76.7 mg (0.401 mmol) 2-(4-methyl-5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (**1l**), 5.5 mg (0.016 mmol, 4.0 mol %) $Co_2(CO)_8$ and 3.3 ml toluene afforded the title compound as two diastereomers (90% overall yield, dr 1.6:1).

Major diastereomer (44.4 mg, mp 80-82 °C, colorless solid): **^{1}H NMR** ($CDCl_3$): δ 7.93 (dd, J = 7.8 Hz, J = 1.6 Hz, 1H), 7.40 (td, J = 7.7 Hz, J = 1.5 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 5.42 (dd, J = 8.0 Hz, J = 5.8 Hz, 1H), 4.26 (quint, J = 6.8 Hz, 1H), 2.38-2.25 (m, 2H), 2.09 (tt, J = 12.9 Hz, J = 7.6 Hz, 1H), 1.76

(dd, J = 12.9 Hz, J = 7.5 Hz, 1H), 1.38 (d, J = 6.4 Hz, 3H). **^{13}C NMR** ($CDCl_3$): δ 161.3, 157.9, 133.9, 128.1, 122.8, 120.1, 116.6, 89.5, 51.8, 29.6, 28.5, 20.4. **IR** (neat, cm^{-1}): 2975, 1662, 1650, 1607, 1470, 1432, 1352, 1179, 1071, 770. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{14}NO_2^+$ ($M + H^+$) 204.1025, found 204.1027.

Minor diastereomer (28.7 mg, mp 115-118 °C, colorless solid): **^{1}H NMR** ($CDCl_3$): δ 7.89 (dd, J = 7.7 Hz, J = 1.5 Hz, 1H), 7.38 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.07 (td, J = 7.5 Hz, J = 0.9 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 5.53 (dd, J = 6.6 Hz, J = 3.6 Hz, 1H), 4.45-4.39 (m, 1H), 2.49-2.41 (m, 1H), 2.29-2.18 (m, 2H), 1.62-1.57 (m, 1H), 1.35 (d, J = 6.5 Hz, 3H). **^{13}C NMR** ($CDCl_3$): δ 160.9, 157.3, 133.8, 128.1, 122.8, 120.5, 116.6, 88.5, 54.0, 30.6, 29.6, 20.7. **IR** (neat, cm^{-1}): 2974, 2902, 1654, 1608, 1423, 1332, 1171, 1073, 769. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{14}NO_2^+$ ($M + H^+$) 204.1025, found 204.1026.

1-Phenyl-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2m)

Following general procedure C using 126 mg (0.497 mmol) 2-(4-phenyl-5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (**1m**), 7.0 mg (0.07 mmol, 4.0 mol %) $Co_2(CO)_8$ and 2.0 ml toluene afforded the title compound as two diastereomers (80% overall yield, dr 2.9:1).

Major diastereomer (78.3 mg, mp 194-197 °C, colorless solid): **^{1}H NMR** ($CDCl_3$): δ 7.91 (dd, J = 7.7 Hz, J = 1.8 Hz, 1H), 7.43 (ddd, J = 8.1 Hz, J = 7.4 Hz, J = 1.7 Hz, 1H), 7.28-7.22 (m, 4H), 7.19-7.16 (m, 1H), 7.08 (td, J = 7.5 Hz, J = 1.0 Hz, 1H), 7.02 (dd, J = 8.2 Hz, J = 1.0 Hz, 1H), 5.62-5.59 (m, 1H), 5.26-5.25 (m, 1H),

2.43-2.29 (m, 3H), 2.00-1.94 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 161.1, 158.2, 141.9, 134.2, 128.8, 128.5, 127.3, 125.9, 122.9, 119.9, 116.8, 89.7, 59.2, 30.8, 29.0. **IR** (neat, cm^{-1}): 3078, 2985, 1668, 1603, 1491, 1464, 1344, 1229, 1065, 855, 768, 698. **HRMS** (ESI) *m/z* calculated for $C_{17}H_{16}NO_2^+$ ($M + H^+$) 266.1181, found 266.1180.

Minor diastereomer (26.8 mg, mp 87-89 °C, colorless solid): **^{1}H NMR** ($CDCl_3$): δ 7.90 (dd, J = 7.7 Hz, J = 1.6 Hz, 1H), 7.43 (ddd, J = 8.3 Hz, J = 7.5 Hz, J = 1.7 Hz, 1H), 7.35-7.31 (m, 2H), 7.26-7.22 (m, 3H), 7.11 (td, J = 7.6 Hz, J = 1.0 Hz, 1H), 6.98 (dd, J = 8.2 Hz, J = 0.9 Hz, 1H), 5.77 (dd, J = 6.2 Hz, J = 2.8 Hz, 1H), 5.47 (dd, J = 7.6 Hz, J = 2.8 Hz, 1H), 2.62-2.52 (m, 1H), 2.42-2.27 (m, 2H), 2.04-1.98 (m, 1H). **^{13}C NMR** ($CDCl_3$): δ 160.9, 157.4, 141.5, 134.1, 128.9, 128.5, 127.4, 125.7, 123.0, 120.2, 116.7, 89.1, 81.2, 31.6, 30.7. **IR** (neat, cm^{-1}): 2971, 2928, 1660, 1608, 1465, 1418, 1433, 1220, 1051, 960, 760, 722. **HRMS** (ESI) *m/z* calculated for $C_{17}H_{16}NO_2^+$ ($M + H^+$) 266.1181, found 266.1181.

1,1-Dimethyl-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2n)

Following general procedure C using 101.6 mg (0.495 mmol) 2-(4,4-dimethyl-5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (**1n**), 7.0 mg (0.02 mmol, 4.0 mol %) $Co_2(CO)_8$ and 2.0 ml toluene afforded the title compound as a colorless solid (100.3 mg, 93%, mp 105-106 °C). **^{1}H NMR** ($CDCl_3$): δ 7.88 (d, J = 7.7 Hz, 1H), 7.36 (dd, J = 8.2 Hz, J = 7.2 Hz, 1H), 7.06 (dd, J = 7.7 Hz, J = 7.2 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 5.46 (t, J = 6.5 Hz, 1H), 2.36-2.29 (m, 1H), 2.25-2.15 (m, 1H), 1.97-1.90 (m, 1H), 1.83-1.75 (m, 1H), 1.59 (s, 3H), 1.53 (s, 3H). **^{13}C NMR** ($CDCl_3$): δ 161.0, 157.5,

133.7, 128.0, 121.0, 116.3, 89.66, 89.64, 62.4, 37.3, 29.1, 28.0, 26.3. **IR** (neat, cm^{-1}): 3070, 2966, 1658, 1608, 1418, 1341, 1071, 786, 720, 598. **HRMS** (ESI) *m/z* calculated for $C_{13}H_{16}NO_2^+$ ($M + H^+$) 218.1181, found 218.1181.

2-Methyl-3,3a-dihydro-1*H*-benzo[*e*]pyrrolo[2,1-*b*][1,3]oxazin-9(2*H*)-one (2o)

Following general procedure C using 95.4 mg (0.499 mmol) 2-(5-methyl-5,6-dihydro-4*H*-1,3-oxazin-2-yl)phenol (**1o**), 7.0 mg (0.07 mmol, 4.0 mol %) $Co_2(CO)_8$ and 2.0 ml toluene afforded the title compound as two diastereomers (80% overall yield, dr 1:1.3).

Major diastereomer (45.2 mg, mp 69-72 °C, colorless solid): **^{1}H NMR** ($CDCl_3$): δ 7.91 (dd, J = 7.8 Hz, J = 1.7 Hz, 1H), 7.40 (ddd, J = 8.2 Hz, J = 7.3 Hz, J = 1.7 Hz, 1H), 7.09 (ddd, J = 7.7 Hz, J = 7.4 Hz, J = 1.1 Hz, 1H), 6.94 (dd, J = 8.2 Hz, J = 1.1 Hz, 1H), 5.49 (dd, J = 7.2 Hz, J = 5.7 Hz, 1H), 3.83 (dd, J = 11.5 Hz, J = 7.8 Hz, 1H), 3.31 (dd, J = 11.5 Hz, J = 8.6 Hz, 1H), 2.55-2.49 (m, 1H), 2.44-2.30 (m, 1H), 1.91 (ddd, J = 12.6 Hz, J = 10.4 Hz, J = 7.2 Hz, 1H), 1.19 (d, J = 6.7 Hz, 3H). **^{13}C NMR** ($CDCl_3$): δ 160.9, 157.5, 133.9, 128.0, 122.8, 119.9, 116.6, 88.7, 50.9, 40.0, 29.5, 18.3. **IR** (neat, cm^{-1}): 2969, 2843, 1659, 1610, 1463, 1430, 1347, 1190, 1057, 760, 696. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{14}NO_2^+$ ($M + H^+$) 204.1025, found 204.1026.

Minor diastereomer (35.9 mg, colorless oil): **^{1}H NMR** ($CDCl_3$): δ 7.90 (d, J = 7.6 Hz, 1H), 7.42-7.38 (m, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 5.52

(dd, J = 6.4 Hz, J = 3.5 Hz, 1H), 4.06 (dd, J = 11.5 Hz, J = 6.8 Hz, 1H), 3.08 (dd, J = 11.4 Hz, J = 7.3 Hz, 1H), 2.56-2.47 (m, 1H), 2.43-2.37 (m, 1H), 2.05-1.98 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H). **^{13}C NMR** ($CDCl_3$): δ 161.0, 157.7, 133.9, 128.2, 122.7, 120.0, 116.6, 88.5, 52.1, 39.8, 30.6, 18.4. **IR** (neat, cm^{-1}): 2959, 2873, 1664, 1610, 1466, 1427, 1355, 1222, 1075, 757, 696. **HRMS** (ESI) *m/z* calculated for $C_{12}H_{14}NO_2^+$ ($M + H^+$) 204.1025, found 204.1023.

4.6.2.4 Crystallographic Data for Major Diastereomer of 2m

Table 4.4 Crystal data and structure refinement for major diastereomer of 2m

Identification code	**2m**	
Empirical formula	$C_{17}H_{15}NO_2$	
Formula weight	265.30	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.4225(4) Å	α = 90°
	b = 13.7700(7) Å	β = 104.075(2)°
	c = 11.5762(5) Å	γ = 90°
Volume	1302.28(11) $Å^3$	
Z	4	
Density (calculated)	1.353 Mg/m^3	
Absorption coefficient	0.089 mm^{-1}	
F(000)	560	
Crystal size	0.30 x 0.25 x 0.20 mm^3	
Theta range for data collection	2.34 to 28.39°	
Index ranges	-11<=h<=11, -18<=k<=17, -11<=l<=15	
Reflections collected	10431	
Independent reflections	3251 [R(int) = 0.0273]	
Completeness to theta = 28.39°	99.4%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9824 and 0.9738	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3251 / 0 / 241	
Goodness-of-fit on F^2	1.074	
Final R indices [I>2sigma(I)]	R1 = 0.0401, wR2 = 0.0962	
R indices (all data)	R1 = 0.0523, wR2 = 0.1032	
Largest diff. peak and hole	0.281 and -0.217 $e/Å^{-3}$	

Table 4.5 Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for major diastereomer of 2m

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	-57(1)	8667(1)	688(1)	25(1)
O(2)	1644(1)	5926(1)	1091(1)	32(1)
N(1)	-353(1)	6991(1)	241(1)	22(1)
C(1)	1596(2)	8533(1)	1105(1)	22(1)
C(2)	2535(2)	9321(1)	1603(1)	28(1)
C(3)	4192(2)	9196(1)	2066(1)	33(1)
C(4)	4913(2)	8291(1)	2043(1)	32(1)
C(5)	3963(2)	7501(1)	1580(1)	27(1)
C(6)	2286(1)	7613(1)	1106(1)	21(1)
C(7)	1202(2)	6753(1)	793(1)	22(1)
C(8)	-1752(2)	6331(1)	62(1)	23(1)
C(9)	-3116(2)	6944(1)	-736(1)	28(1)
C(10)	-2622(2)	7996(1)	-430(1)	29(1)
C(11)	-775(2)	7969(1)	-190(1)	24(1)
C(12)	-2148(1)	6036(1)	1220(1)	20(1)
C(13)	-1647(2)	6567(1)	2264(1)	25(1)
C(14)	-2072(2)	6273(1)	3294(1)	29(1)
C(15)	-3017(2)	5456(1)	3290(1)	30(1)
C(16)	-3531(2)	4924(1)	2252(1)	29(1)
C(17)	-3089(2)	5209(1)	1227(1)	24(1)

Table 4.6 Bond lengths [Å] and angles [°] for major diastereomer of 2m

O(1)-C(1)	1.3703(14)	C(14)-H(14)	0.988(16)
O(1)-C(11)	1.4228(14)	C(15)-C(16)	1.3836(19)
O(2)-C(7)	1.2215(14)	C(15)-H(15)	0.971(16)
N(1)-C(7)	1.3504(15)	C(16)-C(17)	1.3844(18)
N(1)-C(11)	1.4504(15)	C(16)-H(16)	0.958(17)
N(1)-C(8)	1.4623(15)	C(17)-H(17)	0.965(14)
C(1)-C(2)	1.3841(17)		
C(1)-C(6)	1.3932(16)	C(1)-O(1)-C(11)	112.27(9)
C(2)-C(3)	1.3791(19)	C(7)-N(1)-C(11)	121.09(10)
C(2)-H(2)	0.968(15)	C(7)-N(1)-C(8)	124.85(10)
C(3)-C(4)	1.389(2)	C(11)-N(1)-C(8)	114.01(10)
C(3)-H(3)	0.974(17)	O(1)-C(1)-C(2)	117.97(11)
C(4)-C(5)	1.3793(18)	O(1)-C(1)-C(6)	120.77(10)
C(4)-H(4)	0.988(16)	C(2)-C(1)-C(6)	121.10(11)
C(5)-C(6)	1.3935(17)	C(3)-C(2)-C(1)	119.04(12)
C(5)-H(5)	0.979(15)	C(3)-C(2)-H(2)	121.7(8)
C(6)-C(7)	1.4855(16)	C(1)-C(2)-H(2)	119.3(8)
C(8)-C(12)	1.5128(16)	C(2)-C(3)-C(4)	120.70(12)
C(8)-C(9)	1.5393(18)	C(2)-C(3)-H(3)	119.4(10)
C(8)-H(8)	0.951(15)	C(4)-C(3)-H(3)	119.9(10)
C(9)-C(10)	1.5251(18)	C(5)-C(4)-C(3)	120.02(12)
C(9)-H(9B)	0.976(15)	C(5)-C(4)-H(4)	120.4(10)
C(9)-H(9A)	0.982(15)	C(3)-C(4)-H(4)	119.5(10)
C(10)-C(11)	1.5126(17)	C(4)-C(5)-C(6)	120.12(12)
C(10)-H(10B)	0.991(16)	C(4)-C(5)-H(5)	120.8(9)
C(10)-H(10A)	0.995(16)	C(6)-C(5)-H(5)	119.0(9)
C(11)-H(11)	1.011(14)	C(1)-C(6)-C(5)	118.95(11)
C(12)-C(13)	1.3879(16)	C(1)-C(6)-C(7)	119.49(10)
C(12)-C(17)	1.3889(16)	C(5)-C(6)-C(7)	120.77(11)
C(13)-C(14)	1.3867(18)	O(2)-C(7)-N(1)	123.63(11)
C(13)-H(13)	0.978(15)	O(2)-C(7)-C(6)	123.15(11)
C(14)-C(15)	1.3771(19)	N(1)-C(7)-C(6)	112.97(10)

N(1)-C(8)-C(12)	112.67(9)	O(1)-C(11)-H(11)	106.9(8)
N(1)-C(8)-C(9)	101.65(9)	N(1)-C(11)-H(11)	109.5(8)
C(12)-C(8)-C(9)	112.72(10)	C(10)-C(11)-H(11)	114.9(7)
N(1)-C(8)-H(8)	109.5(9)	C(13)-C(12)-C(17)	118.71(11)
C(12)-C(8)-H(8)	107.5(9)	C(13)-C(12)-C(8)	122.96(11)
C(9)-C(8)-H(8)	112.8(8)	C(17)-C(12)-C(8)	118.31(10)
C(10)-C(9)-C(8)	105.07(10)	C(14)-C(13)-C(12)	120.49(12)
C(10)-C(9)-H(9B)	113.0(9)	C(14)-C(13)-H(13)	120.1(8)
C(8)-C(9)-H(9B)	111.5(9)	C(12)-C(13)-H(13)	119.4(8)
C(10)-C(9)-H(9A)	111.0(9)	C(15)-C(14)-C(13)	120.41(12)
C(8)-C(9)-H(9A)	108.4(9)	C(15)-C(14)-H(14)	120.3(9)
H(9B)-C(9)-H(9A)	107.8(12)	C(13)-C(14)-H(14)	119.3(9)
C(11)-C(10)-C(9)	103.27(11)	C(14)-C(15)-C(16)	119.56(12)
C(11)-C(10)-H(10B)	112.2(9)	C(14)-C(15)-H(15)	121.1(9)
C(9)-C(10)-H(10B)	111.8(9)	C(16)-C(15)-H(15)	119.4(9)
C(11)-C(10)-H(10A)	108.7(9)	C(15)-C(16)-C(17)	120.16(12)
C(9)-C(10)-H(10A)	110.8(9)	C(15)-C(16)-H(16)	119.6(9)
H(10B)-C(10)-H(10A)	109.9(13)	C(17)-C(16)-H(16)	120.2(9)
O(1)-C(11)-N(1)	110.83(9)	C(16)-C(17)-C(12)	120.66(11)
O(1)-C(11)-C(10)	110.75(10)	C(16)-C(17)-H(17)	119.7(8)
N(1)-C(11)-C(10)	103.95(10)	C(12)-C(17)-H(17)	119.6(8)

Symmetry transformations used to generate equivalent atoms.

Table 4.7 Anisotropic displacement parameters ($Å^2x10^3$) for major diastereomer of 2m

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	25(1)	18(1)	31(1)	-4(1)	5(1)	1(1)
O(2)	32(1)	18(1)	45(1)	0(1)	8(1)	2(1)
N(1)	24(1)	17(1)	24(1)	-1(1)	7(1)	-3(1)
C(1)	24(1)	20(1)	21(1)	1(1)	7(1)	-1(1)
C(2)	33(1)	19(1)	33(1)	-3(1)	9(1)	-3(1)
C(3)	33(1)	28(1)	37(1)	-4(1)	6(1)	-9(1)
C(4)	24(1)	34(1)	36(1)	1(1)	5(1)	-4(1)
C(5)	26(1)	26(1)	29(1)	1(1)	9(1)	1(1)
C(6)	25(1)	20(1)	20(1)	-1(1)	8(1)	-1(1)
C(7)	26(1)	19(1)	23(1)	-2(1)	10(1)	0(1)
C(8)	25(1)	19(1)	23(1)	-4(1)	6(1)	-4(1)
C(9)	29(1)	30(1)	23(1)	1(1)	1(1)	-6(1)
C(10)	27(1)	26(1)	31(1)	4(1)	1(1)	0(1)
C(11)	29(1)	19(1)	23(1)	1(1)	5(1)	-2(1)
C(12)	19(1)	18(1)	23(1)	1(1)	3(1)	1(1)
C(13)	25(1)	23(1)	26(1)	-4(1)	7(1)	-4(1)
C(14)	31(1)	31(1)	25(1)	-5(1)	8(1)	-1(1)
C(15)	32(1)	32(1)	28(1)	3(1)	12(1)	0(1)
C(16)	28(1)	25(1)	34(1)	1(1)	9(1)	-5(1)
C(17)	24(1)	23(1)	25(1)	-3(1)	3(1)	-3(1)

Table 4.8 Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for major diastereomer of 2m

	x	y	z	U(eq)
H(2)	2010(17)	9943(11)	1631(12)	28(4)
H(3)	4860(20)	9748(12)	2417(14)	41(4)
H(4)	6100(20)	8211(12)	2401(14)	40(4)
H(5)	4445(18)	6852(11)	1599(13)	31(4)
H(8)	-1519(17)	5755(11)	-317(12)	27(4)
H(9B)	-4188(19)	6783(11)	-607(13)	29(4)
H(9A)	-3142(18)	6801(11)	-1572(14)	35(4)
H(10B)	-3116(19)	8443(12)	-1091(14)	37(4)
H(10A)	-2931(18)	8200(11)	310(14)	33(4)
H(11)	-322(16)	8097(10)	-908(12)	21(3)
H(13)	-986(17)	7152(10)	2269(12)	25(3)
H(14)	-1685(19)	6653(11)	4033(14)	35(4)
H(15)	-3327(19)	5245(12)	4006(14)	38(4)
H(16)	-4180(19)	4353(13)	2251(14)	40(4)
H(17)	-3423(17)	4823(11)	512(12)	28(4)

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